BRIEFING MATERIALS

FOR

JOINT MEETING OF

THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND THE PEDIATRIC ADVISORY COMMITTEE

MAY 17-18, 2011

Advisory Committee Briefing Materials; Available for Public Release

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EXECUTIVE SUMMARY

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1 EXECUTIVE SUMMARY

McNeil Consumer Healthcare Division of McNeil-PPC, Inc. (McNeil) is a major manufacturer of over-the-counter (OTC) drug products, including pediatric Tylenol® and Motrin® analgesic and antipyretic products. As a major manufacturer of OTC pediatric products, McNeil is committed to encouraging the appropriate and safe use of medicines in children, including adding new dosing information on the OTC pediatric acetaminophen label to assist caregivers and healthcare providers in appropriately dosing children, especially those 6 to 23 months of age, and identifying interventions intended to address root causes of unintentional acetaminophen exposures and medication errors.

The Food and Drug Administration (FDA) announced that it will hold a public joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee on May 17 and 18, 2011. The committees intend to discuss and consider the following:

- Adding new dosing information for oral over-the-counter (OTC) drug products containing acetaminophen to the label for children less than 2 years of age.
- Adding a weight-based dosing regimen to the existing age-based dosing regimen for children 2 to <12 years of age.
- Ways that administration by caregivers can be improved so that medication errors can be minimized.

On February 1, 1999, McNeil submitted (Docket 77N-0094) a Citizen Petition under 21 CFR 10.30 and 330.10 to request that the FDA amend the directions for use covering pediatric acetaminophen products in the Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Anti-rheumatic (IAAA) Drug Products for OTC Human Use to expand the age groups (ie, to less than 2 years of age) for OTC consumer dosing instructions.

In this briefing book, McNeil provides scientific evidence and information to address and support its request. McNeil strongly supports FDA's adding additional pediatric dosing information on the OTC label to assist caregivers and healthcare professionals to appropriately use and consistently dose acetaminophen. This Executive Summary includes relevant background and regulatory history regarding OTC acetaminophen pediatric dosing and McNeil's perspectives and proposals for 1) adding dosing for acetaminophen to the OTC label for children 6 to 23 months of age and 2) adding weight-based dosing for acetaminophen to age-related dosing for ages 6 months to less than 12 years of age. In addition, it highlights key support for each of McNeil's proposals; further details are provided in the Sections 2 to 8 of this briefing book.

1.1 Background and Regulatory History: OTC Pediatric Acetaminophen Dosing

There is wide recognition of acetaminophen's well-established safety and efficacy when used as directed as an antipyretic/analgesic medicine for the treatment of fever and mild-to-moderate pain in children and infants. In the United States, approximately 23% of children less than two years of age are given single-ingredient acetaminophen by caregivers in the previous week [1]. Practicing healthcare professionals routinely recommend acetaminophen use for the temporary, symptomatic relief of fever and pain in children, including those less than 2 years of age.

Acetaminophen has been marketed in OTC formulations for children since 1959. In 1977, an FDA OTC Advisory Review Panel included pediatric dosage schedules of acetaminophen in its recommendations to be included in the IAAA OTC monograph.

McNeil has long supported developing evidence-based dosing information for OTC pediatric single-ingredient analgesic/antipyretic medicines. In 1983, McNeil, based on available evidence, published an OTC pediatric acetaminophen dosing schedule using standard weight-based and age-related dosing increments [2]. The schedule was designed to provide a dose range of 10 to 15 mg/kg per single dose. Since 1984, McNeil and other OTC companies have voluntarily provided weight-based dosing in addition to the proposed OTC monograph age-related dosing directions on OTC single-ingredient acetaminophen labels for children 2-11 years of age. Also, single-ingredient acetaminophen dosing schedules for children less than 2 years have been and continue to be made available to healthcare professionals.

In 1988, FDA issued its OTC IAAA TFM, which provides for an age-related dosing schedule for single-ingredient acetaminophen products for children 2 years of age and older. Table 1-1 provides FDA's 1988 OTC IAAA TFM pediatric acetaminophen dosage schedule for children 2 years of age and older.

Table 1-1. Pediatric Acetaminophen Dosage Schedule: 1988 FDA OTC IAAA TFM

Age (years)	Number of 80 mg dosage units (mg)	Number of 325 mg dosage units
Under 2	Consult a doctor	Consult a doctor
2 to < 4	2 (160)	½
4 to < 6	3 (240)	¾
6 to < 9	4 (320)	1
9 to < 11	4-5 (320-400)	1 to 1 ¼
11 to < 12	4-6 (320-480)	1 to 1 ½
Doses may be repeated every 4 hours while symptoms persist, up to 5 times a day or as directed by a doctor		

Previous FDA Nonprescription Drugs Advisory Committees (NDAC) meetings have supported OTC pediatric dosing topics relevant to this upcoming FDA meeting:

- In 1995, NDAC agreed without dissent that the preferred basis for determining OTC pediatric dosage should be weight, if it is known, but age ranges should also be given for those where weight is not known.
- In 1997, NDAC unanimously recommended that single-ingredient analgesic/antipyretic products (ie, acetaminophen and ibuprofen) could be safely and effectively labeled for children less than 2 years of age, focusing on a minimum patient age of 6 months for which dosing information could appear on OTC labeling.

In April 1999, FDA approved dosing directions on the consumer OTC label for children 6 to 23 months of age for McNeil's OTC Infants' Motrin (ibuprofen) product. FDA's approved dosing schedule for OTC pediatric ibuprofen includes both weight-based and age-related dosing with a dose increment for 12-17 lbs body weight and ages 6-11 months and a dose increment for 18-23 lbs body weight and ages 12-23 months.

In June 2009, FDA convened a Joint Meeting of the Drug Safety and Risk Management, Nonprescription Drug and Anesthetic and Life Support Drugs Advisory Committees regarding potential methods of addressing the risk of acetaminophen-related overdose and liver injury. As part of a report provided to the Advisors from FDA's Center for Drug Evaluation and Research (CDER) Acetaminophen Hepatotoxicity Working Group (issued February 26, 2008), recommendations were made for the inclusion of acetaminophen dosing instructions for children less than 2 years of age.

1.2 McNeil's Citizen Petition: Expand OTC Acetaminophen Label Dosing Directions to Less Than 2 Years of Age

On February 1, 1999, McNeil submitted (Docket 77N-0094) a Citizen Petition (CP) under 21 CFR 10.30 and 330.10 to request that the Commissioner of Food and Drugs amend the directions for use covering pediatric acetaminophen products in the TFM for IAAA Drug Products for OTC Human Use to expand the age groups for OTC consumer dosing instructions. Specifically, McNeil requested to provide dosing instructions for acetaminophen on the consumer OTC label for children less than 2 years of age. The OTC TFM for IAAA does not provide for OTC acetaminophen dosing instructions for children less than 2 years of age.

Following a meeting between FDA and McNeil in September 2000 and at FDA's request, McNeil amended its Citizen Petition in August 2001 with additional information regarding its proposed weight ranges for accompanying age ranges (Docket No. 77N-0094.

Comment No. CP14). McNeil's amendment to its 1999 Citizen Petition recommends the following for OTC single-ingredient acetaminophen-containing products for children:

- Provide an age-related dose schedule for 6 to 23 months of age
- Provide a weight-based dose schedule for the full range of pediatric weights (12 pounds [lbs] and higher), ie, ages 6 months to less than 12 years
- Provide a statement to the effect that when dosing children, dosing by weight is preferred, and that only if weight is not known should the age-related schedule be used.

McNeil has also requested that FDA allow professional labeling for healthcare professionals for dosing of children less than 6 months of age and under 12 pounds (lbs.) body weight. On April 22, 2010, at the request of FDA, McNeil provided available pharmacokinetic and clinical trial data supporting OTC acetaminophen dosing for children 6 to 23 months of age. The sub-sections that follow highlight McNeil's perspectives and key support for its specific proposals.

1.2.1 McNeil's Perspective and Proposal: Add Dosing for Acetaminophen to the OTC Label for Children 6 to 23 Months of Age

This section provides an overview of the following topics that are detailed more fully in later sections (as noted) of the briefing book including: the need for single-ingredient acetaminophen and OTC dosing labeling in children less than 2 years of age (Section 2), acetaminophen clinical trial efficacy and safety evidence (Section 3 – Efficacy; Section 5 – Clinical Trial Safety) and pharmacokinetic evaluations (Section 4). These data support amending the directions for use covering pediatric acetaminophen products in the OTC IAAA TFM by expanding the age group to 6 to 23 months for OTC consumer dosing instructions.

1.2.1.1 Need for OTC Acetaminophen Dosing

As detailed in Section 2, there is a clear medical and caregiver need for acetaminophen medicines in the pediatric population, including children less than 2 years of age. Children, including those less than 2 years of age, experience pain and fever that is effectively relieved by symptomatic treatment with acetaminophen. The course of fever and pain and the indications for treatment with acetaminophen are similar in younger and older children. Acetaminophen is the most commonly recommended and used antipyretic and analgesic medicine in children 6 to 23 months of age.

Appropriate acetaminophen dosing directions should be made available on the OTC label for caregivers who are already using this medicine on their own or under guidance

of a healthcare provider for the relief of their child's fever and pain. Expanding the OTC label to include acetaminophen dosing directions for children 6 to 23 months age can help minimize medication errors in the following ways:

- Helps caregivers find the correct dose to give to their child.
- Reduces the need for caregivers to call a doctor, a friend, or a relative for a dose, or to rely on their limited recall of previous dose recommendations, or guess at the dose.
- Allows caregivers to confirm the dose when provided by the doctor or other healthcare professional.

1.2.1.2 Clinical Efficacy and Safety of Acetaminophen in Children

In 1983, Temple determined that the maximum temperature decrement and the duration of antipyretic effect increased with increasing doses of acetaminophen. Temple's analysis demonstrated that in order to achieve a temperature decrement in excess of 1ºC (1.8ºF) lasting for at least 4 hours, a dose of at least 10 mg/kg was necessary and recommended the dose be in the range of 10-15 mg/kg. As detailed in Section 3, extensive antipyretic efficacy data from clinical trials support the single OTC dose of acetaminophen of 10-15 mg/kg for children. Figure 1-1 illustrates the dose-response between 10-15 mg/kg and 20-30 mg/kg. Mean temperature decrement over time is shown for acetaminophen doses of 10-15 mg/kg from 13 trials and 20-30 mg/kg from 3 trials. A reference line at 1ºC temperature decrement is shown.

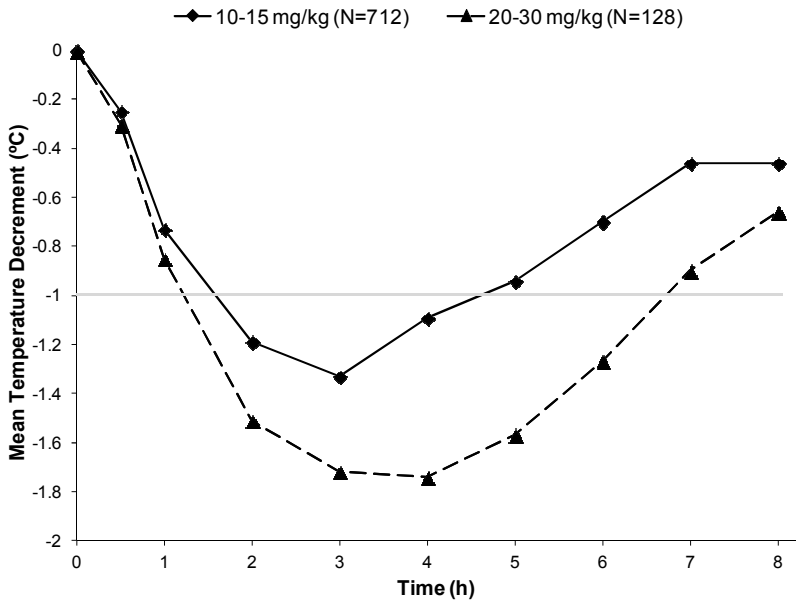
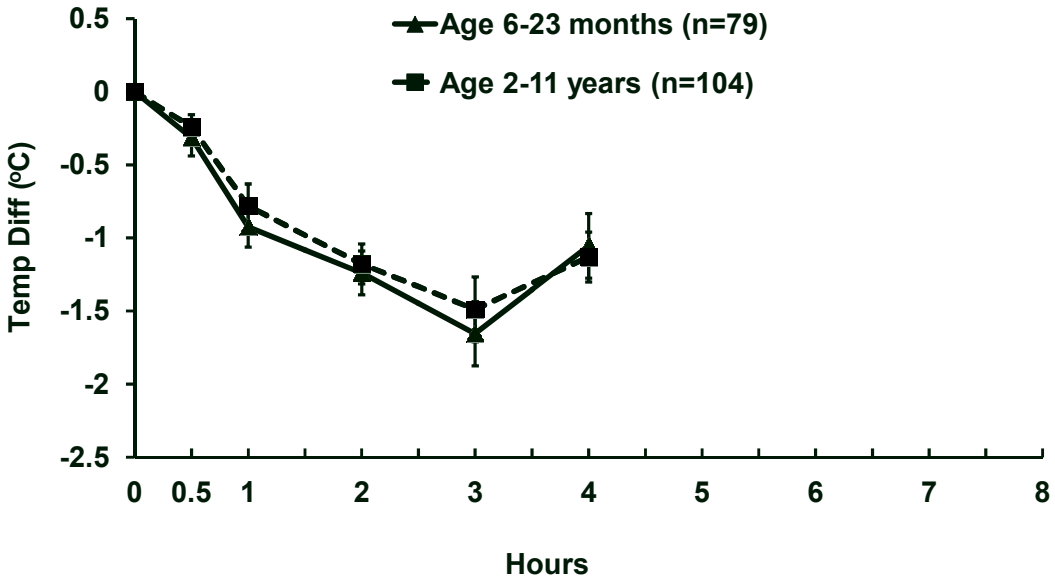


Figure 1-1. Cross-Study Comparison of Mean Temperature Decrement Over Time by Dose of Acetaminophen

Clinical trials have confirmed the antipyretic and analgesic efficacy of the 10-15 mg/kg dose in children 6 to 23 months of age. In clinical trials, the course of fever and its response to the same mg/kg doses of acetaminophen is similar in children 6 to 23 months of age and children 2 to 11 years of age. Four studies, 2 single dose (86-639, 82-222) and 2 multiple dose (80-220, 86-640), were identified with available data for subjects both less than 2 years of age and 2 years of age and older. Figure 1-2 presents the mean change from baseline up to 4 hours where all 4 studies have been combined. The time up to 4 hours was used because this represented the single dose period for all studies.



Studies 80-220, 82-222, 86-639 & 86-640

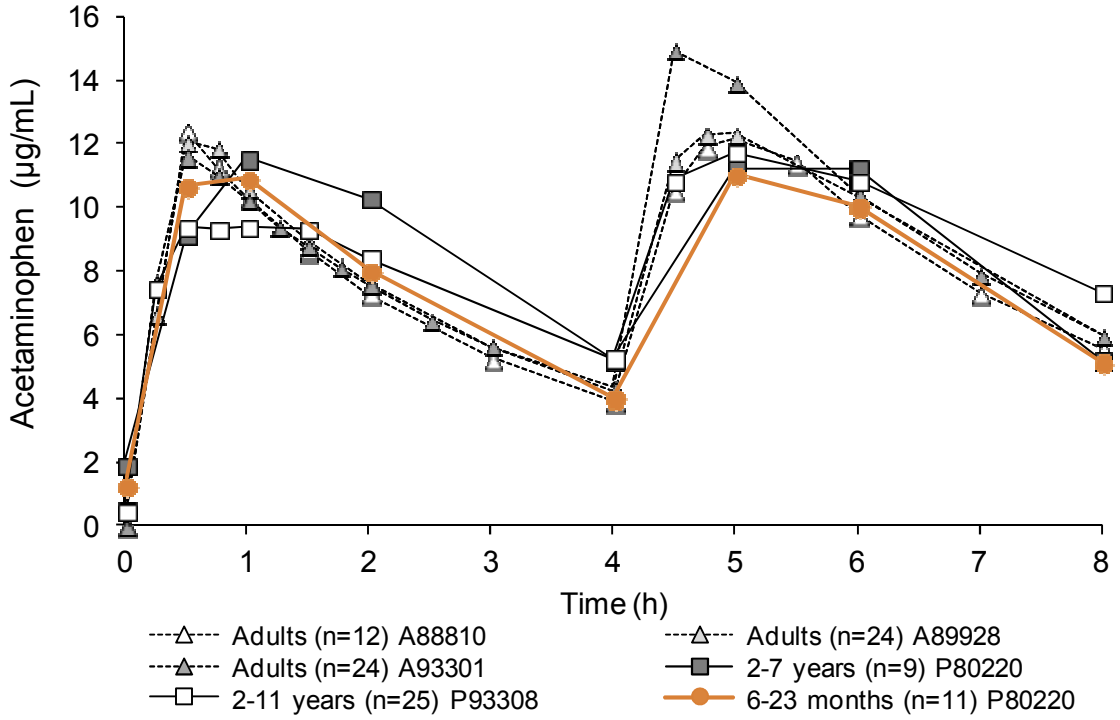
Figure 1-2. Reduction in Mean Body Temperature (95% CI) with Acetaminophen 10-15 mg/kg by Age Group for Studies 80-220, 82-222, 86-639, 86-640

As detailed in Section 5, the safety of acetaminophen dosed at 10-15 mg/kg is well established from clinical trials in children, including children 6 to 23 months of age, and is not different when compared with older children. When used according to the OTC label at single doses in the range of 10-15 mg/kg up to 5 times per day (75 mg/kg/day), acetaminophen is an effective and generally well-tolerated analgesic and antipyretic medicine for children.

1.2.1.3 Pharmacokinetic Profiles and Pharmacodynamics of Pediatric Acetaminophen

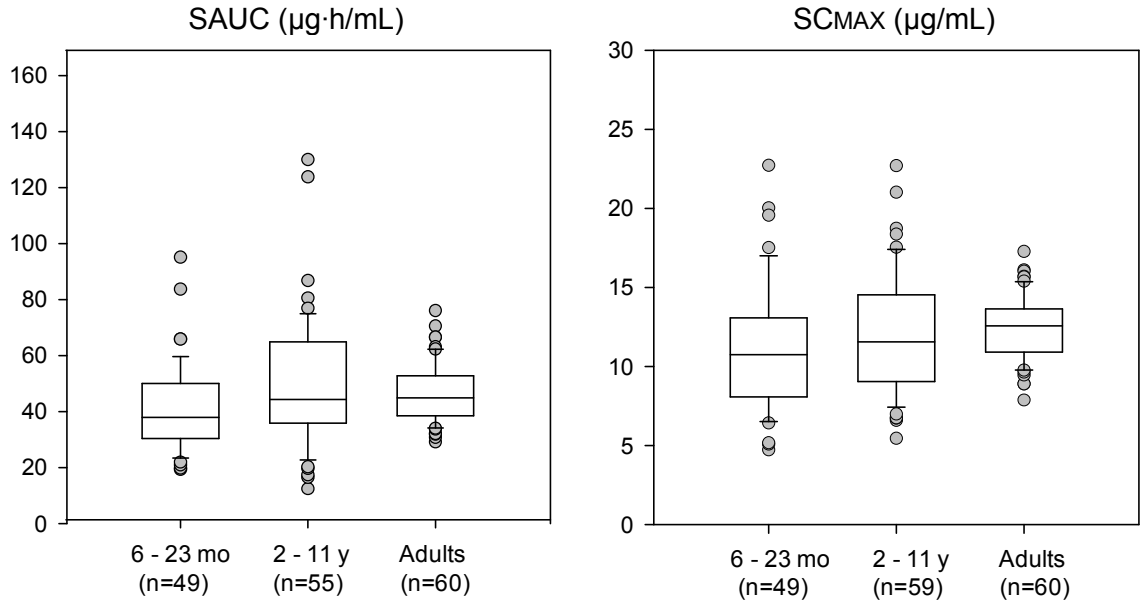
As described in Section 4, in 6 of 9 pooled studies, children and adults received two 10-15 mg/kg doses of an acetaminophen oral liquid four hours apart, and the mean pharmacokinetic profiles are displayed in Figure 1-3 by age group and study. Overall these data illustrate that the concentration-time curves were similar among adults and both pediatric age groups.

Figure 1-3. Mean Pharmacokinetic Profiles of Two 10-15 mg/kg Doses of Acetaminophen Oral Liquid by Age Group and Study



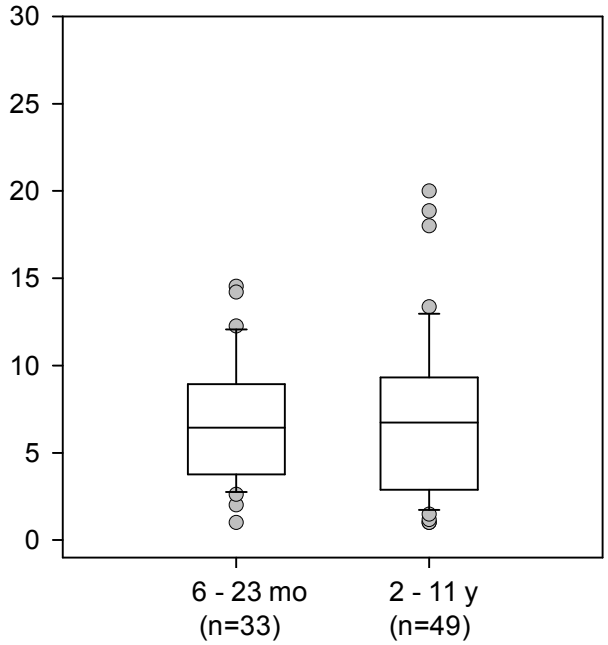
An integrated analysis of acetaminophen exposure across multiple McNeil-sponsored pediatric and adult studies demonstrated that the effective 10-15 mg/kg dose provided children ages 6-23 months with comparable exposure as that in children ages 2-11 years. For the primary analysis of exposure among age groups, individual exposure values for children who received the 20-30 mg/kg dose were standardized to the 10-15 mg/kg dose by dividing by 2 (SAUC and SC_{MAX}). Box plots that include median, 25th and 75th percentiles for SAUC and SC_{MAX} by age group are shown in Figure 1-4. These plots show that acetaminophen exposures for children 6-23 months and 2-11 years are comparable, although the variability was higher for children 2-11 years. There appears to be slightly higher median exposures and less variability for the adult group.

Figure 1-4. Box Plot Comparison of Acetaminophen Exposure in 5 Fever Studies and 1 Immunization Study by Age Group Standardized to the 10-15 mg/kg Dose



A pharmacokinetic-pharmacodynamic integrated analysis of acetaminophen concentration-response data across multiple McNeil-sponsored pediatric fever studies showed that the EC50 for children ages 6-23 months is similar to children 2-11 years (Figure 1-5). This is the first report of acetaminophen concentration-response data in children ages 6-23 months.

Figure 1-5. Box Plot Showing Comparable Acetaminophen Concentrations Needed for a 50% Reduction in Fever, or EC50 (µg/mL), by Age Group



Extrapolation of broader antipyretic and analgesic efficacy of acetaminophen from children 2 to 11 years of age to children 6 to 23 months is appropriate. From the multiple-dose pharmacokinetic data, the average concentration of acetaminophen at steady state measured in children, ages 6 months to 6 years, was 10.8 ± 4.1 µg/mL for the 12-15 mg/kg doses given every four hours. This average concentration has been linked to both antipyretic and analgesics responses consistently across studies and populations, and further supports McNeil's proposed OTC dosing instructions for children ages 6 months to < 2 years.

1.2.1.4 Professional Support

There is broad support from professionals for adding dosing directions to the OTC labeling for acetaminophen medicines for children less than 2 years of age. Professional associations currently support (Table 1-2) and a recent survey shows pediatricians support including dosing for children less than 2 years of age on the OTC label (Section 2.5).

Table 1-2. Professional Associations Supporting Dosing Directions on the OTC Label for Children Less Than 2 Years of Age

Association	Statements
American Academy of Pediatrics (AAP)	In 2011, stated the following in its instructions for caregivers for the treatment of fever and antipyretic use in children: "It is critically important for pediatricians to clearly describe the appropriate use (ie, formulation, dose, and dosing interval) of acetaminophen and ibuprofen to caregivers (Table 1). Child safety will be further enhanced by clear labeling and the development of simplified dosing methods, standardized drug concentrations, and standardized dosing devices." [3] AAP's healthychildren website for caregivers currently contains a section on medications used to treat fever which states: "Acetaminophen can be given without a doctor's advice once your child is older than three months, and ibuprofen can be given to children older than six months of age." In addition, an acetaminophen dosing chart is provided by age and weight for children 0-5 months, 6-11 months, and 1-2 years. It is noted that dosing for fever should be based on current weight and that age is provided as a convenience only. [4]
American Academy of Family Physicians [5]	In May 2007, stated the following in their submission to the docket for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Use; Proposed Amendment of the Tentative Final Monograph; Required Warnings and Other Labeling: "Importantly, AAFP urges that FDA expand OTC labeling of pediatric acetaminophen products to include dosing for children less than 2 years of age. AAFP believes that providing care givers with complete dosing information will decrease the cases of misadministration and potentially decrease situations of overdose in young children."
American Pharmacists Association (APhA) [6]	At the September 19, 2002 FDA Nonprescription Drugs Advisory Committee (NDAC) meeting concerning safety issues related to acetaminophen, the APhA stated the following in their presentation in reference to manufacturers of OTC products and their revision of labeling for their acetaminophen products to emphasize the active ingredient and include an overdose warning: "APHA encourages the FDA to recognize the industry's efforts in this area and to further advance their efforts by allowing important dosing information for patients under the age of two to be added to the product label. The inclusion of this dosing information may prevent overdoses caused by inaccurate dose estimates."
American Association of Poison Control Centers (AAPCC) [7]	In 1997, AAPCC stated the following at the 1997 FDA NDAC meeting in support of lowering the age limit for OTC analgesics and antipyretics down to at least 6 months: "Dosing instructions on the label of OTC products could provide parents and caretakers with a readily available reference to help remind them of the proper dose to administer. Without these important data on the label, dosing instructions would be neither standardized nor controlled."

In addition, medical and pharmaceutical reference textbooks provide weight-based acetaminophen dosing (10-15 mg/kg) for children less than 2 years of age (Table 1-3).

Table1-3. Summary of Pediatric Acetaminophen Dosing < 2 Years of Age as Reported in Pharmaceutical Reference Textbooks

Year	Reference Source	Weight	Age	Dosing Provided for Children < 2 Years of Age
2007	Nelson Textbook of Pediatrics [8]	Yes	--[a]	Yes
2009	Current Diagnosis & Treatment Pediatrics [9]	Yes	--	--
2009	Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care [10]	Yes	--	Yes
2009	The Harriet Lane Handbook: A Manual for Pediatric House Officers [11]	Yes	Yes	Yes
2009	Martindale: The Complete Drug Reference [12]	Yes	Yes	Yes
2011	AHFS Drug Information 2011 [13]	Yes	Yes	Yes
2011	Drug Facts and Comparisons 2011 [14]	Yes	Yes	Yes

a: -- = not mentioned in textbook.

1.2.1.5 McNeil's Proposal

McNeil's current acetaminophen dosing chart and directions (Table1-4) on Infants' Tylenol Drops product directs caregivers to ask a doctor for acetaminophen dosing in children less than 2 years of age and under 24 pounds of weight. For children ages 2-3 years, this dosing chart provides both weight-based and age-related dosing instruction.

Table 1- 4. Current McNeil Dosing Chart and Directions: OTC Infants' Concentrated Tylenol Drops (80 mg Acetaminophen/0.8 mL)

- Find right dose on chart below. If possible, use weight to dose; otherwise, use age.

Dosing Chart

Weight (lb)	Age (yr)	Dose (mL)
under 24	under 2 years	ask a doctor
24-35	2-3 years	1.6 mL (0.8 mL + 0.8 mL)

McNeil's proposed acetaminophen dosing chart and directions provides weight-based and age-related dosing for children 6 to 23 months of age on the OTC label, including a dose increment for ages 6-11 months and a dose increment for 12-23 months of age. (Table 1-5). Caregivers are directed to ask a doctor for acetaminophen dosing in children less than 6 months of age. McNeil's proposed dosing chart would not include ages 2-3 years on the Infants' OTC acetaminophen label, consistent with pediatric ibuprofen labeling.

Table 1- 5. Proposed McNeil Dosing Chart and Directions: OTC Infants' Tylenol Oral Suspension for Children (160 mg Acetaminophen/5 mL)

- Find right dose on chart below. If possible, use weight to dose; otherwise, use age.

Dosing Chart

Weight (lbs)	Age (months)	Dose (mL)
under 6 months		ask a doctor
12-17 lbs	6-11 months	2.5 mL
18-23 lbs	12-23 months	3.75 mL

It is important to note that McNeil and the OTC industry are transitioning to a single concentration of 160 mg per 5 milliliters for OTC pediatric liquid single-ingredient acetaminophen products later this year.

Adding dosing directions for 6 to 23 months of age on the OTC label of acetaminophen infant's product and transitioning to a single concentration of 160 mg acetaminophen per 5 milliliters for OTC pediatric acetaminophen liquid products are important elements of McNeil's proposed Risk Management Plan to help reduce pediatric OTC acetaminophen medication errors (Section 8).

1.2.2 McNeil Perspective and Proposal: Add Weight-Based Dosing for Acetaminophen to Age-Related Dosing for Ages 6 Months to Less Than 12 Years

This section summarizes relevant history, development of weight-based dosing (Section 7), pharmacokinetic modeling of OTC dosing schedules (Section 4), and professional support and caregiver research (Section 6). These data support amending the OTC IAAA TFM to add weight-based dosing to existing age-related dosing for OTC acetaminophen dosing directions for weights 12 pounds and higher, ie, ages 6 months to less than 12 years.

1.2.2.1 Relevant History

In 1983, Temple published a novel pediatric acetaminophen dosing schedule which included both weight-based and age-related dosing, and was designed to produce doses more closely correlated to the targeted dosing range of 10-15 mg/kg than previously available schedules [2].

Since 1984, McNeil and other OTC companies have voluntarily provided weight- based dosing along with the proposed OTC monograph age-related pediatric acetaminophen dosing directions on OTC single-ingredient acetaminophen labels for children 2 through 11 years of age. Also, single-ingredient acetaminophen weight-based and age- related dosing schedules for children less than 2 years have been and continue to be made available to healthcare professionals.

While weight-based dosing for OTC antipyretic/analgesics was considered in FDA's rule-making process, only age-related acetaminophen dosing is included in FDA's 1988 OTC IAAA TFM. At that time, FDA stated that a children's dosing schedule based on age was acceptable for the following reasons: age-based pediatric dosing correlates with doses based on body surface area, the average consumer will more readily understand age-based, and that consumers usually know age but not always weight.

In 1995, an FDA Nonprescription Drugs Advisory Committee agreed without dissent that the preferred basis for determining OTC pediatric dosage should be weight, if it is known, but age ranges should also be given for those where weight is not known. Subsequently, in April 1999, FDA approved an OTC weight-based and age-related dosing schedule on the consumer OTC label for children 6 to 23 months of age for McNeil's OTC Infants' Motrin (ibuprofen) product.

1.2.2.2 Weight-Based Dosing Remains Within 10-15 mg/kg Target

As detailed in Section 7, the McNeil proposed weight-based and age-related dosing schedules for acetaminophen were designed with the goal of consistently producing a dose within the 10-15 mg/kg range for children across all weights and ages. Figure 1-6 presents the approximate doses (mg/kg) of acetaminophen produced by using McNeil's proposed dosing chart for children 6-23 months of age (Table 1-5) for single-ingredient pediatric acetaminophen liquids intended for use on OTC label of infants' products. When compared with age-related dosing (Section 7, Figure 7-4) which provides a dose ***near*** the target range of 10-15 mg/kg, weight-based dosing provides a dose which remains ***within*** the 10-15 mg/kg range, and should therefore be considered the preferred dosing schedule when a child's weight is known. Weight-based dosing should be the

preferred method for selecting a dose because it avoids the variability inherent to the age-based dosing, caused by differing body sizes among children of the same age.

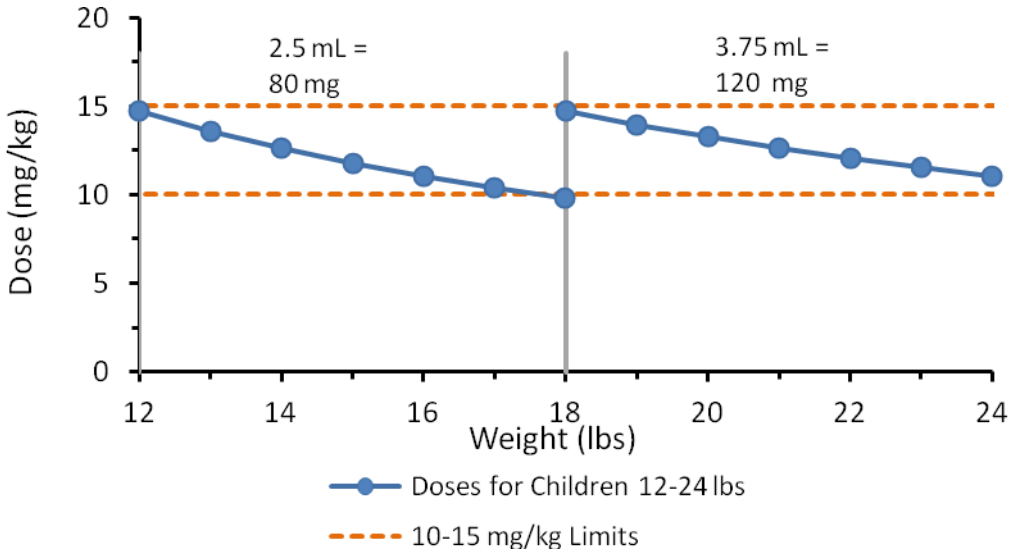


Figure 1-6. McNeil's Proposed Dosing for Ages 6-23 Months: Comparison of Weight-Based Acetaminophen Doses in Children Weighing 12-23 pounds to Optimal Dosage Range of 10-15 mg/kg

Figure 1-7 presents the approximate doses (mg/kg) of acetaminophen produced by using McNeil's proposed dosing chart for children ages 2-11 years (Table 1-7) for single-ingredient pediatric acetaminophen liquids intended for use on OTC label of children's products. When the age-related dosing (Section 7, Figure 7-2), which provides a dose ***near*** the target range of 10-15 mg/kg, is compared with the weight-based dosing, which remains ***within*** the 10-15 mg/kg range, it is clear that weight-based dosing should be considered the preferred dosing schedule when a child's weight is known.

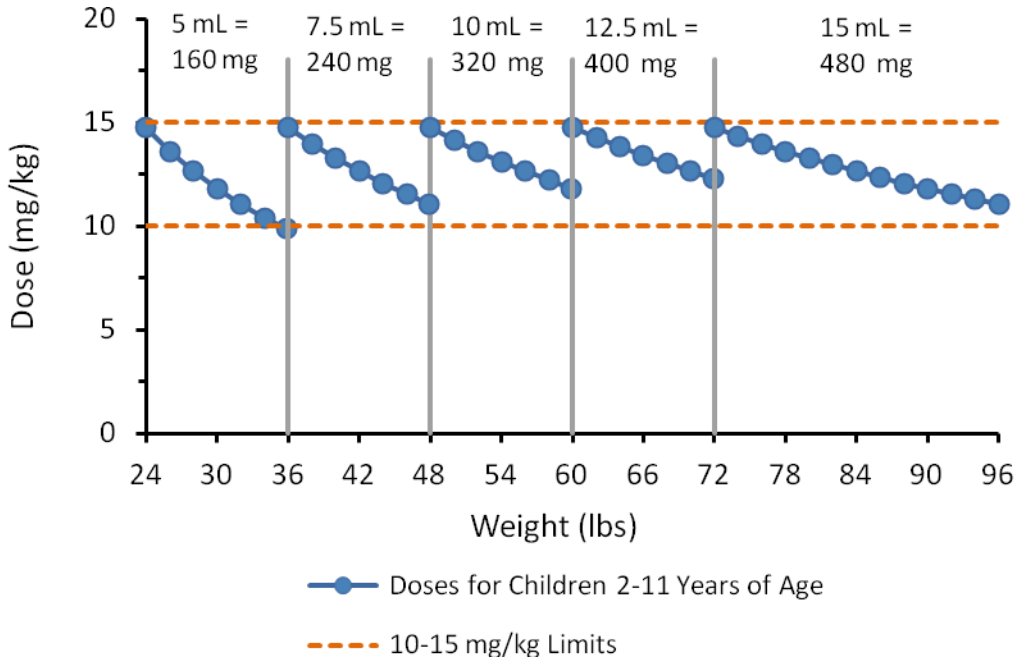


Figure 1-7. McNeil's Proposed Dosing for Ages 2-11 Years – Comparison of Weight-Based Acetaminophen Doses for Children Weighing 24 to 95 pounds to Optimal Dosage Range of 10-15 mg/kg

While weight-based dosing refines dosing, there is no evidence of an altered risk-benefit profile when only age-related dosing is used for acetaminophen. Comparisons in Section 7 indicate that weight-based and age-related dosing schedules for children 6 months to 11 years of age are acceptable for labeling of acetaminophen products.

1.2.2.3 Pharmacokinetic Modeling Supports Weight-Based and Age-Related Dosing

As detailed in Section 4, evaluation of McNeil's proposed pediatric OTC acetaminophen dosing charts was conducted by simulating AUC with a population pharmacokinetic model. The model that describes acetaminophen exposure and accounts for age and body size effects on clearance and McNeil pediatric data were used to evaluate the proposed OTC doses for children 6 23 months. The cohort of children ages 2-11 years provided reference range for acetaminophen exposure. Simulations show that both the proposed weight-based and age-related charts provide appropriate doses for children ages 6-23 months by maintaining acetaminophen exposure close to the reference exposure range in the older children.

1.2.2.4 Professional Support

As detailed in Section 6, pediatricians and professional associations support adding a weight-based dosing schedule to the OTC pediatric acetaminophen label. They recommend using the weight-based dosing schedule when weight is known and limiting age-related dosing to use when weight is not known. As summarized in Table 1-6, professional associations recommend weight-based dosing for acetaminophen in children.

Table 1-6. Professional Associations that Recommend Weight-Based Dosing of Acetaminophen in Infants and Children

Association	Statements
American Academy of Pediatrics (AAP)	• Supports the use of antipyretics to improve the comfort of the febrile child. States that acetaminophen doses of 10 to 15 mg/kg per dose given every 4 to 6 hours orally are generally regarded as safe and effective. [3] • Caregivers who understand that dosing should be based on weight rather than age or height of fever are much less likely to give an incorrect dose. [3] • AAP's healthychildren website for caregivers currently contains a section on medications used to treat fever which states: "Acetaminophen can be given without a doctor's advice once your child is older than three months, and ibuprofen can be given to children older than six months of age." In addition, an acetaminophen dosing chart is provided by age and weight for children 0-5 months, 6-11 months, and 1-2 years. It is noted that dosing for fever should be based on current weight and that age is provided as a convenience only. [4]
International Evidence-Based Group for Neonatal Pain [15]	• Recommends the use of acetaminophen for postoperative pain associated with circumcision. States that the recommended analgesic dose for neonates is 10 to 15 mg/kg orally or 20 to 30 mg/kg rectally.

In March 2011, McNeil conducted an internet survey of 152 pediatricians who spent at least 25% of their time in direct patient care and who recommended OTC pain/fever relievers containing acetaminophen for children 12 years of age or younger in an average week [16]. Ninety-eight percent and 97% of pediatricians preferred that weight-based dosing be included on the OTC single-ingredient acetaminophen label, either alone or in combination with age for infants' and children's medicines, respectively. Only 2% and 3% of pediatricians preferred that medication directions instruct caregivers to determine the correct dose for their child based on age alone. For infants' medicines, 70% of pediatricians preferred weight alone, whereas for children's medicines, the

percentages were similar for pediatricians that preferred weight alone (52%) and those that preferred weight and age (45%).

1.2.2.5 Caregiver Research Supports Both Weight-Based and Age-Related Dosing Charts

Caregivers prefer weight-based dosing and consumer testing confirms the addition of weight-based dosing does not complicate caregivers' ability to select a correct dose compared to age-related dosing only. Consumer research also shows that weight-based dosing is important to caregivers for infants and children and that many use weight to dose when doses by age and weight are discordant. The following caregiver research findings are further detailed in Section 6:

- Most caregivers (91%) select the correct dose with an infants' weight and age dosing chart with two 40 mg dosing increments.

- When given two infants' dosing charts, one with dosing instructions for ages 6 to 23 months and a second that says "ask a doctor", and asked which provides the information they need to select a correct dose for their child:
    - 91% of caregivers chose the dosing chart with 6 to 23 month instructions
    - 5% of caregivers chose the dosing chart that says "ask a doctor"

- Caregivers want both age and weight information to provide the information needed to select a correct dose for their child. When asked which is the most important for selecting a correct dose for their child, caregivers responded as follows:
    - 80% of caregivers believe weight is most important for selecting a dose
    - 4% of caregivers believe both weight and age are equally important
    - 15% of caregivers believe age is most important for selecting a dose

1.2.2.6 McNeil Proposal

McNeil's proposed acetaminophen dosing chart for children ages 2 to 11 years (Table 1-7) is the same as its current acetaminophen dosing chart, using the same weight-based and age-related dose increments. One difference is the ordering of the volumetric dosing measures on the chart: "mL" is first in order and then followed by "tsp" in the Dose section of the proposed chart. This is consistent with the Consumer Healthcare Products Association (CHPA) voluntary guidelines for volumetric measures on pediatric liquid medicines.

Table 1- 7. McNeil Proposed Dosing Directions and Chart: Children's Tylenol Liquid Suspension (160 mg Acetaminophen/5 mL)

- Find right dose on chart below. If possible, use weight to dose; otherwise, use age.

Weight (lb)	Age (yr)	Dose (mL or tsp)
under 24	under 2 years	ask a doctor
24-35	2-3 years	5 mL (1 tsp)
36-47	4-5 years	7.5 mL (1 ½ tsp)
48-59	6-8 years	10 mL (2 tsp)
60-71	9-10 years	12.5 mL (2 ½ tsp)
72-95	11 years	15 mL (3 tsp)

mL = milliliter; tsp = teaspoonful

McNeil's proposed acetaminophen dosing chart and directions with weight-based and age-related for children 6 to 23 months of age is provided in Table 1-5.

1.3 McNeil's Proposed Risk Management Program: Addressing Root Causes of Unintentional Acetaminophen Exposures and Overdose

In June 2009, FDA convened a Joint Meeting of the Drug Safety and Risk Management, Nonprescription Drug and Anesthetic and Life Support Drugs Advisory Committees regarding potential methods of addressing the risk of acetaminophen-related overdose and liver injury in both adults and pediatrics.

As provided in Section 8, data from multiple sources including McNeil's post-marketing database, the AAPCC and the Consumer Product Safety Commission's National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance (NEISS-CADES) confirm that accidental unsupervised ingestions are the most common root cause of unintentional acetaminophen exposures and overdoses in children. Medication errors, although much less common than accidental unsupervised ingestions, can result in pediatric medication errors with acetaminophen for various reasons:

- Administering greater than the recommended dose
- Dosing of infants' concentrated drops at children's liquid dose
- Use of multiple acetaminophen-containing medicines
- Prescribing or dispensing errors
- Administering more frequently than labeled
- Administration of adult medicine

1.3.1 McNeil's Program Targets Accidental Unsupervised Ingestions and Medication Errors

McNeil is committed to working with FDA and other stakeholders to proactively address and reduce unintentional acetaminophen exposures and overdose in children. Following FDA's June 2009 Advisory Committee meeting, McNeil submitted to FDA (Docket No. FDA-2009-N-0138) a proposed risk management program aimed to reduce acetaminophen-related liver injury (Section 8). McNeil's plan for infants and children targets accidental unsupervised ingestions and medication errors and includes the following key elements:

- Transition to a single concentration of 160 mg acetaminophen per 5 milliliters for OTC pediatric acetaminophen liquid products
- Include in-pack validated dosing device (already included in all McNeil pediatric liquid OTC acetaminophen-containing products) and flow restrictor in all pediatric liquid OTC acetaminophen products; establish a requirement for "Directions" OTC labeling
- Add dosing directions for 6 to 23 months of age on OTC label of acetaminophen infant's product; communicate new dosing directions to consumers and healthcare professionals
- Standardize dosing abbreviations and volumetric measures in dosing directions for all OTC pediatric products for pain and fever relief; include weight and age dosing
- Evaluate and test enhanced messages ("Don't use adult medicines in children" and "Don't give more than the recommended dose" and "Keep medicines out of reach of children")
- Support scientific research and surveillance designed to provide additional data and enhance our understanding of acetaminophen exposure, overdose and liver injury.

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SECTION 2
NEED AND SUPPORT FOR EXPANDED PEDIATRIC ACETAMINOPHEN DOSING FOR CHILDREN LESS THAN 2 YEARS OF AGE

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2 NEED AND SUPPORT FOR EXPANDED PEDIATRIC ACETAMINOPHEN DOSING FOR CHILDREN LESS THAN 2 YEARS OF AGE

McNeil's request to expand the pediatric age groups for OTC consumer dosing instructions for acetaminophen by adding dosing directions for children 6 months to less than 2 years of age to infants' products is supported by medical need, extensive use, pediatrician and professional association recommendations, and results of caregiver and professional research as summarized in the following sections.

2.1 FDA Working Group Recommendation from 2008

The FDA's Acetaminophen Hepatotoxicity Working Group from the Center for Drug Evaluation and Research provided written recommendations for FDA interventions to potentially help reduce unintentional overdose with OTC acetaminophen medicines and decrease the occurrence of acetaminophen hepatotoxicity (February 26, 2008). One of recommendations of the working group was to include dosing instructions for children under 2 years of age if accurate dosing instructions can be determined and adequate efficacy data exist to support dosing.

2.2 Key Points

- There is a clear medical and caregiver need for acetaminophen medicines in the pediatric population, including children less than 2 years of age.
    - Children, including those less than 2 years of age, experience pain and fever that is effectively relieved by symptomatic treatment with acetaminophen.
    - Healthcare professionals routinely recommend acetaminophen to caregivers for use in children, including infants.
    - Survey data indicate extensive use of acetaminophen in children less than 2 years of age.
    - Given this extensive use without labeling, it is anticipated that adding this dosing information for children 6 to 23 months of age to the OTC label will not increase exposure of young children to acetaminophen, and has the potential to lessen the risks that may occur with its unlabeled use.
- Consumer research shows that caregivers obtain dosing information from multiple and potentially conflicting sources.
- Expanding the OTC label to include acetaminophen for children 6 to 23 months of age can help minimize medication errors in the following ways:
    - Helps caregivers find the correct dose to give their child.

  - Reduces the need for caregivers to call a doctor, a friend, or a relative for a dose, or to rely on their limited recall of previous recommendations, or guess at the dose.
  - Allows caregivers to confirm the dose when provided by the doctor or other healthcare professional.
- Pediatricians and other healthcare professionals support providing acetaminophen dosing directions on OTC medicines for children less than 2 years of age.
  - Recent (2009) research indicates that 92% of pediatricians agreed that providing dosing instructions on the label for children 12 to 23 pounds/6 to 23 months of age would increase a caregiver's ability to dose accurately.
  - Professional associations support the inclusion of dosing information for children less than 2 years of age on the product label.
- Providing OTC acetaminophen dosing directions for children less than 2 years of age on the consumer labeling would be consistent with what is already available on OTC ibuprofen medicines for children less than 2 years of age.
- The implementation of the proposed OTC acetaminophen dosing for children ages 6 to 23 months is an important element in reducing medication errors, is supported by the pediatric healthcare community, and is consistent with previous FDA Advisory Committee reviews of the proposal.

2.3 Medical Need and Extensive Use of Acetaminophen in Pediatric Populations Including Children Less Than 2 years of Age

2.3.1 Pediatricians Recommend Acetaminophen for Children

There is a clear medical need for pediatric analgesic and antipyretic medicines in children 6 to 23 months of age. Acetaminophen is used for symptomatic treatment of pain and fever in children under the age of 2 years. According to the American Academy of Pediatrics (AAP), most children will experience eight to 10 colds in the first 2 years of life [1]. Acetaminophen is recommended by AAP for the treatment of fever associated with a cold when a child is very uncomfortable [1] and for use in relieving mild-to-moderate pain in children with acute otitis media by both AAP and the American Academy of Family Physicians [2]. Pediatricians individually also recommend use of acetaminophen in children less than 2 years of age. A comparison of pediatrician recommendations for acetaminophen or ibuprofen in 2009 and in 2010 for children less than 2 years of age indicated that 76% of pediatric recommendations in this age group were for acetaminophen and 24% were for ibuprofen.

2.3.2 Professional Associations and Healthcare Groups Recommend Acetaminophen for Children

As summarized in Table 2- 1, professional associations and healthcare groups recommend the use of acetaminophen in infants and children at doses and frequency consistent with current OTC labeling.

Table 2- 1. Professional Associations and Healthcare Groups Recommending Acetaminophen for Use in Children Less Than 2 years of Age

Association/Group	Statements
American Academy of Pediatrics [3,4]	• Supports the use of antipyretics to improve the comfort of the febrile child. States that acetaminophen doses of 10 to 15 mg/kg per dose given every 4 to 6 hours orally are generally regarded as safe and effective. Also states a lower age limit of 3 months, unless specifically recommended by a healthcare provider for the younger patient and, then, only after the infant has been examined by a healthcare provider. [3] • Prevention and Management of Pain in the Neonate: Acetaminophen should not be used alone for severe pain, but can be considered for use during the later postoperative period, after minor procedures, or as adjunct to other measures. [4]
CDC - Immunization Practices Advisory Committee (ACIP) [5]	• The report states that evidence does not support use of antipyretics before or at the time of vaccination; however, they can be used for the treatment of fever and local discomfort that might occur following vaccination.
American Academy of Pediatrics and American Academy of Family Physicians [2]	• Recommends the use of acetaminophen or ibuprofen for treatment of acute otitis media pain. States that these medications provide effective analgesia for mild to moderate pain, are readily available, and are a mainstay of pain management for acute otitis media. States the importance of the management of pain, especially during the first 24 hours of an episode of acute otitis media.
International Evidence-Based Group for Neonatal Pain [6]	• Recommends the use of acetaminophen for postoperative pain associated with circumcision. States that the recommended analgesic dose for neonates is 10 to 15 mg/kg orally or 20 to 30 mg/kg rectally.
Institute for Clinical Systems Improvement [7]	• Recommends the use of acetaminophen for the treatment/management of viral upper respiratory infections in infants greater than 3 months, children, and adolescents.
Cincinnati Children's Hospital Medical Center [8]	• Recommends the use of an appropriate analgesic including oral agents (acetaminophen or ibuprofen) or topical ear drops (anesthetic or Naturopathic herbal Extract Ear Drops) for the management/treatment in children age 2 months up to 13 years of age who present with signs and symptoms of acute otitis media.

Table 2- 1. Professional Associations and Healthcare Groups Recommending Acetaminophen for Use in Children Less Than 2 years of Age

Association/Group	Statements
University of Michigan Health System [9]	• Recommends the use of analgesics (ibuprofen, acetaminophen, topical analgesics) for the management of acute otitis media in pediatric patients greater than 2 months old.

A summary of recent recommendations for weight-based and age-related pediatric acetaminophen dosing reported in pharmaceutical textbooks, many of which provide dosing for children less than 2 years of age, is provided in Section 6, Table 6-3.

2.3.3 Slone Survey Indicates Extensive Use of Pediatric Acetaminophen Medicines

The Slone Survey [10] was a population-based national telephone household survey of medication use conducted by the Slone Epidemiology Unit (Slone) of Boston University School of Public Health. The survey was conducted during the period from February 1998 through April 2007 and provided recent information from parents/guardians on 2857 children 0 to 11 years of age for use of all medications, including prescription and OTC drugs, vitamins and minerals, and herbal preparations/supplements during the 1-week period preceding a telephone interview. For the full years of the survey (1999 through 2006), enrollment per year ranged from 277 to 436 subjects.

Table 2- 2 shows the Slone Survey data for percent of use of single-ingredient acetaminophen and ibuprofen during the 7 days before the interview by pediatric age group. Twenty-three percent of children less than 2 years of age had been given single-ingredient acetaminophen in the week prior to interview compared with 7.2% for single-ingredient ibuprofen. This extensive use of acetaminophen in children less than 2 years of age, even when that use is currently unlabeled, supports the need for dosing directions on the OTC label. It also supports that allowing labeling for this age group will not likely increase exposures.

Table 2- 2. Percent Use of Single-Ingredient Acetaminophen and Ibuprofen OTC Medications in Children (N=2857) during the 7 Days Prior to Interview, 1998-2007 (Slone Survey)

		Acetaminophen	Ibuprofen
Age Group (Years)	N	%	%
< 2	478	23.0%	7.2%
2 to 5	1000	7.7%	7.2%
6 to 11	1379	8.6%	7.3%

Table 2- 3 provides additional detail from the Slone Survey on the use of acetaminophen and ibuprofen in children including those less than 2 years of age. Data are provided on use of acetaminophen alone, ibuprofen alone, and use of both acetaminophen and ibuprofen during the 7 days before the interview. Use of acetaminophen alone was reported for 20% of infants less than 6 months of age, with no use of ibuprofen reported in this age group. Use of acetaminophen alone was reported in 28% of children 6 to 11 months, 21% of children 12 to 23 months, 10% of children 24 to 35 months, and 8.5% of children ≥36 months.

Table 2- 3. Percent Use of Acetaminophen and Ibuprofen OTC Medications in Children (N=2857) during the 7 Days Prior to Interview - More Detailed Age Groups Below 36 Months of Age, 1998-2007 (Slone Survey)

Age Group (Months)	Acetaminophen Alone %	Ibuprofen Alone %	Both Acetaminophen and Ibuprofen %
0 to 5	20	0	0
6 to 11	28	6.1	5.9
12 to 23	21	4.9	3.5
24 to 35	10	8.2	2.4
≥ 36	8.5	5.9	1.2

2.4 Current Sources for, and Issues with, Pediatric Dosing Information for Consumers

2.4.1 Consumer Research Shows Caregivers Obtain Dosing Information from Multiple Sources

Caregivers obtain information on OTC pediatric dosing from various sources. Two studies conducted in emergency departments in the United States in 1986 and 1998 reported on sources of dosing information for OTC medications. These studies indicated that caregivers decided on the dose to give their child based on the following: physicians, nurses, family, packaging, previous use, and guessing. It should be noted that these studies were conducted before there was widespread use of the internet. It is likely that current data would include the internet as source of dosing information for some caregivers.

Gribetz and Cronley [11] reported data from 88 caregivers of young children seen at the Children's Hospital of Philadelphia, Pennsylvania, during a 5-day period in March 1986. Parents were eligible for the survey if their child was less than or equal to 5 years of age and one of the parental complaints was a perceived or measured fever. The mean age of the children was 22.7 months. It was reported that most of the parents were black and the majority received medical assistance. Sixty percent of the caregivers had

completed high school. Information including acetaminophen dose was provided by the mother 95% of the time. When asked, "Where did you get dose information?", the responses were as follows: physician (61%), bottle (31%), nurse (1%), self/family (1%), and other (6%).

Li et al [12] reported on data from 200 caregivers seen at the pediatric emergency department at Jacobi Medical Center in Bronx, New York, during a 6-week period from May 1998 to July 1998. Parents were eligible for the survey if their child was 10 years of age or younger and had been given acetaminophen or ibuprofen within the past 24 hours. The mean age of the children was 34 months. Mean caregiver age was 31 years. The sources of dosing information were: doctor (55%), package labeling (28%), guessing (8%), or dose based on the last time medication was given (4%).

The internet is an additional, more recent source of acetaminophen dosing information used by caregivers. McNeil recently (February 28, 2011) identified 16 websites that provided pediatric dosing information (milliliters or teaspoonfuls to give to a child by age and/or weight of the child) for acetaminophen using Google and the following search terms: acetaminophen dosage for infants, Tylenol dosage for infants, acetaminophen dosage for children, and Tylenol dosage for children. Review of these websites indicated that 13 (81%) of the 16 websites contained dosing information for children less than 2 years of age. Six (46.1%) of the 13 websites provided dosing information for children less than 2 years of age based only on weight, 1 website provided dosing information only by age, and the remaining 6 (46.1%) websites provided dosing based on age and weight. Two (15.4%) of the 13 websites with dosing information for children less than 2 years of age did not provide dosing information consistent with that which McNeil provides to healthcare professionals. Both of these sites provided dosing information based only on weight, 1 with higher doses (askdrsears.com) and 1 with lower doses (stlouischildrens.org) compared with Tylenol professional dosing information. Three of the 16 websites did not provide dosing information on children less than 2 years of age; these 3 websites provided both weight-based and age-related dosing. These data support providing accurate FDA-approved weight-based and age-related dosing information on the product label in an effort to minimize inconsistency, potential confusion, and medication errors.

2.5 Professional Perspectives and Need for Expanded OTC Labeling for Children Ages 6 to 23 months

2.5.1 Professional Research Indicates Pediatricians Support Expanded Labeling

McNeil conducted an online (internet) study of 200 pediatricians during the period from June 18, 2009 through June 22, 2009 [13]. The objective of this study was to explore

pediatricians' reactions to having dosing directions on OTC single-ingredient Tylenol pediatric product labeling for children ages 6 to 23 months. When asked if dosing instructions on the label for children 12 to 23 pounds/6 to 23 months of age would increase caregivers' ability to dose accurately, 91.5% indicated yes, 7% indicated no, and 1.5% indicated that they did not know.

These data are consistent with the results of an earlier survey conducted by McNeil in 1999 in a nationwide sample of 225 pediatricians [14]. In this survey, 92% of pediatricians reported personally supporting the idea of consumer labeling on pediatric analgesic packages for dosing of patients under 2 years of age.

2.5.2 Professional Associations Support Adding Dosing Directions to the OTC Labeling for Children 6 to 23 Months of Age

As summarized in Table 2- 4, there is broad support from professional associations for adding dosing directions to the OTC labeling for acetaminophen medicines for children less than 2 years of age.

Table 2- 4. Professional Associations Supporting Dosing Directions on the OTC Label for Children Less Than 2 Years of Age

Association	Statements
American Academy of Pediatrics (AAP)	In 2011, stated the following in its instructions for caregivers for the treatment of fever and antipyretic use in children: "It is critically important for pediatricians to clearly describe the appropriate use (ie, formulation, dose, and dosing interval) of acetaminophen and ibuprofen to caregivers (Table 1). Child safety will be further enhanced by clear labeling and the development of simplified dosing methods, standardized drug concentrations, and standardized dosing devices." [3] AAP's healthychildren website for caregivers currently contains a section on medications used to treat fever which states: "Acetaminophen can be given without a doctor's advice once your child is older than three months, and ibuprofen can be given to children older than six months of age." In addition, an acetaminophen dosing chart is provided by age and weight for children 0-5 months, 6-11 months, and 1-2 years. It is noted that dosing for fever should be based on current weight and that age is provided as a convenience only. [15]
American Academy of Family Physicians [16]	In May 2007, stated the following in their submission to the docket for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Use; Proposed Amendment of the Tentative Final Monograph; Required Warnings and Other Labeling: "Importantly, AAFP urges that FDA expand OTC labeling of pediatric acetaminophen products to include dosing for children less than 2 years of age. AAFP believes that providing care givers with complete dosing information will decrease the cases of misadministration and potentially decrease situations of overdose in young children."

Table 2- 4. Professional Associations Supporting Dosing Directions on the OTC Label for Children Less Than 2 Years of Age

Association	Statements
American Pharmacists Association (APhA) [17]	At the September 19, 2002 FDA Nonprescription Drugs Advisory Committee (NDAC) meeting concerning safety issues related to acetaminophen, the APhA stated the following in their presentation in reference to manufacturers of OTC products and their revision of labeling for their acetaminophen products to emphasize the active ingredient and include an overdose warning: "APHA encourages the FDA to recognize the industry's efforts in this area and to further advance their efforts by allowing important dosing information for patients under the age of two to be added to the product label. The inclusion of this dosing information may prevent overdoses caused by inaccurate dose estimates."
American Association of Poison Control Centers (AAPCC) [18]	In 1997, AAPCC stated the following at the 1997 FDA NDAC meeting in support of lowering the age limit for OTC analgesics and antipyretics down to at least 6 months: "Dosing instructions on the label of OTC products could provide parents and caretakers with a readily available reference to help remind them of the proper dose to administer. Without these important data on the label, dosing instructions would be neither standardized nor controlled."

2.6 Summary

Labeling of single-ingredient acetaminophen medicines with dosing instructions for children 6 to 23 months of age would provide important information to caregivers that would help decrease caregiver confusion and facilitate proper use and administration of the correct dose. Expanded labeling would also reduce the need for caregivers to call a doctor, a friend, or a relative for a dose, or to rely on their limited recall of previous recommendations, or guess at the dose, and would allow caregivers to confirm the acetaminophen dose provided by the doctor or other healthcare professional.

In addition, labeling of single-ingredient acetaminophen medicines with dosing instructions for children 6 to 23 months of age will result in enhanced prevention of an identified root cause of acetaminophen dosing errors. These dosing errors are discussed more fully in Section 8, Root Causes of Unintentional Acetaminophen Exposures and Overdose, and McNeil's Risk Mitigation Plan.

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SECTION 3
EFFICACY OF ACETAMINOPHEN AND DOSING IN CHILDREN

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3 EFFICACY OF ACETAMINOPHEN AND DOSING IN CHILDREN

An acetaminophen dose of 10-15 mg/kg is the appropriate dose for children. Early studies indicated that low doses of 5 mg/kg were not clinically effective and that doses of at least 10 mg/kg were needed to achieve an adequate clinical effect in fever. A review of subsequent unpublished McNeil data confirms this conclusion as does a review of 39 published trials.

Clinical trials have confirmed the antipyretic efficacy of the 10-15 mg/kg dose in children 6 to 23 months of age. In clinical trials, the course of fever and its response to the same mg/kg doses of acetaminophen is similar in children 6 to 23 months of age and children 2 to 11 years of age.

3.1 Key Points

- Extensive antipyretic efficacy data from clinical trials support the single OTC dose of acetaminophen of 10-15 mg/kg for children.
- Clinical trials have confirmed the antipyretic efficacy of the 10-15 mg/kg dose in children 6 to 23 months of age. In clinical trials, the course of fever and its response to the same mg/kg doses of acetaminophen is similar in children 6 to 23 months of age and children 2 to 11 years of age.
- Acetaminophen 10-15 mg/kg has also been shown to be an effective analgesic in children 6 to 23 months of age.

3.2 Historical Dose-Response Data Leading to the Selection of 10-15 mg/kg as the Appropriate Single Dose for Acetaminophen

Prior to 1980, acetaminophen was dosed in a range that varied between 3.9 and 12.7 mg/kg for children 1 to 12 years of age based on age-related dosing.

In 1976, German researchers, Windorfer and Vogel [1], published data from 26 febrile children between 1.5 to 8 years of age who were treated with 3 different doses of acetaminophen, 5 mg/kg, 10 mg/kg and 20 mg/kg. They concluded that the 5 mg/kg acetaminophen dose did not produce clinically statistically significant antipyresis.

In 1983, Temple published a review of 5 pediatric fever studies [2], including the data from Windorfer and Vogel. Based on the data from the 5 studies reviewed and their comparative efficacy, it was determined that the maximum temperature decrement and the duration of antipyretic effect increased with increasing doses of acetaminophen. Temple's analysis demonstrated that in order to achieve a temperature decrement in

excess of 1ºC (1.8ºF) lasting for at least 4 hours, a dose of at least 10 mg/kg was necessary and recommended the dose be in the range of 10-15 mg/kg.

Wilson and colleagues in the US [3] assessed acetaminophen dosing in the range of 10-15 mg/kg by modeling data from 18 febrile children between 3 to 5 years of age and suggested that an average dose of 13.3 mg/kg would produce adequate antipyresis with respect to time of onset, maximum temperature decrement and duration of fever reduction.

Table 3-1 summarizes the comparison of the antipyretic effect of acetaminophen 5 mg/kg, 10 mg/kg, and 20 mg/kg adapted from 5 studies in Temple's 1983 review.

Table 3-1. Comparison of Antipyretic Effect of Various Acetaminophen Doses

Dose [Ref]	Initial temperature (°C)	Mean temperature decrement (°C) (Hours following administration)								Maximum decrement (°C)
		0.5	1.0	2.0	3.0	4.0	5.0	6.0	8.0	
5 mg/kg [1]	39.5	0.3	0.4	0.4	0.3	0.4	0.1	-	0.1	0.4
10 mg/kg [1[1],4,5,6,7]	39.5	0.3	0.8	1.5	1.6	1.4	1.1	1.2	0.9	1.6
20 mg/kg [1,6]	39.6	0.4	1.4	1.9	-	2.0	-	-	1.9	2.0

Figure 3-1 displays the cross-study comparison of the mean temperature decrement for acetaminophen doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg. A reference line at 1ºC temperature decrement is shown.

[1] References are cited individually to provide the reader with a link to the reference citation in the electronic version of the document.

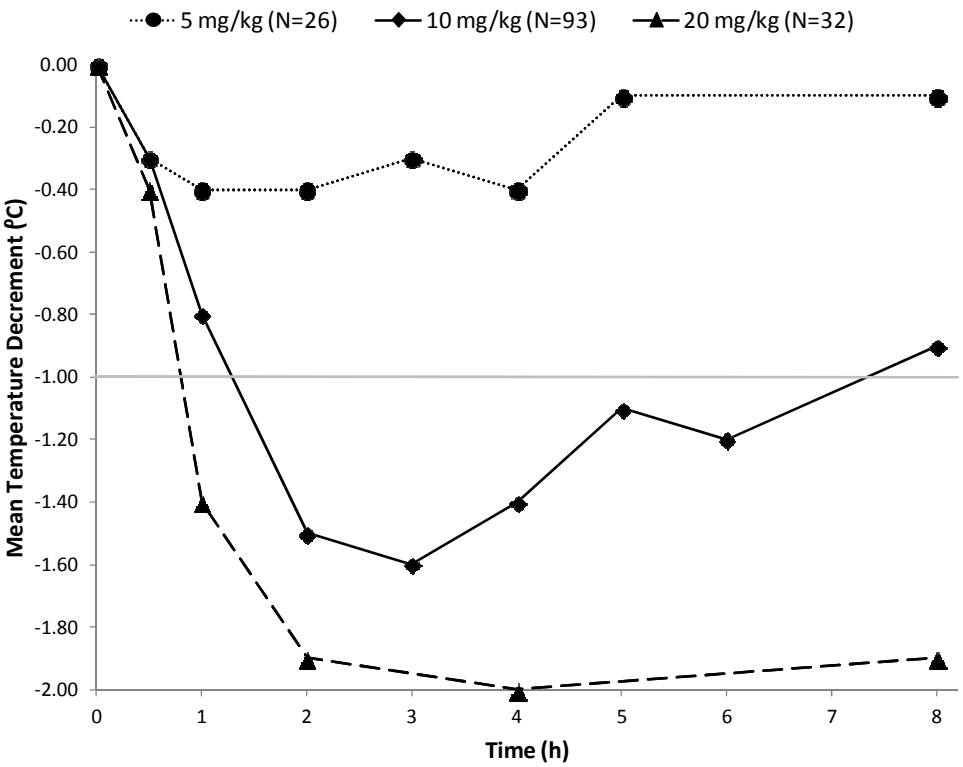


Figure 3-1. Mean Temperature Decrement with Acetaminophen Doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg

Based on these data, the dose range of 10-15 mg/kg has been used for acetaminophen doses on the OTC label for children 2 to 11 years of age and has been used by pediatricians and other healthcare providers when dosing children less than 2 years of age, where dosage is not provided on the OTC label.

3.3 Additional Dose Response Data Supporting 10-15 mg/kg as an Appropriate Single Dose for Acetaminophen

Since the 1983 review, many other clinical studies have evaluated and confirmed that an acetaminophen dose of 10-15 mg/kg is appropriate for children from 6 months to 11 years of age.

We identified 13 unpublished McNeil studies and 39 published studies from a review of trials published during 1980 to 2010 that had 1 or more oral acetaminophen-only treatment arms and evaluated pediatric dosing of acetaminophen for the treatment of fever in which there was detailed data about temperature decrements over time following drug administration. Table 3-2 provides a summary of the number of subjects in the unpublished and published studies.

Table 3-2. Summary Tabulation of Unpublished McNeil Clinical Studies and Published Studies of Acetaminophen

Study Type	Number of Studies	Number of Acetaminophen Subjects
Unpublished Studies	13	840
Included children <2 y	5	
Included children ≥2 y	13	
Published Studies	39	2185
Included children <2 y	30	
Included children ≥2 y	37	

The 13 unpublished studies contained both 12.5 mg/kg single-dose data (10-15 mg/kg) and 25.0 mg/kg single-dose data (20-30 mg/kg). The 13 unpublished studies included 10 studies that investigated 1 dose of acetaminophen and 3 studies that investigated 2 doses of acetaminophen. These 13 studies involved 840 children receiving acetaminophen for treatment of fever.

The 39 published studies included 37 studies that investigated 1 dose of acetaminophen and 2 studies that investigated 2 doses of acetaminophen. These 39 studies involved 2185 children receiving acetaminophen for treatment of fever. The studies were categorized into 5 different dosing tiers and were analyzed by dose category.

3.3.1 Dose Response Data From Unpublished McNeil Consumer Healthcare Clinical Trials

A comprehensive review of unpublished clinical trials conducted by McNeil was undertaken to identify studies that evaluated the antipyretic efficacy of acetaminophen, either compared to placebo or to another antipyretic/analgesic agent and the doses used. All clinical study reports for McNeil's antipyretic studies completed between 1980 and 2010 were reviewed. Studies which had at least 1 oral acetaminophen-only treatment arm were identified. All studies were included whether they also included a placebo or active treatment controls, but only the data on acetaminophen is presented. Additional methodology surrounding these unpublished clinical trials can be found in Section 3.8.

Altogether the trials enrolled 840 children treated with acetaminophen ranging from 6 months to 11 years of age. There were 712 children who received a 10-15 mg/kg dose and 128 children who received a 20-30 mg/kg dose. Eleven were single-dose studies and the other 2 contained a single-dose component. The unpublished trials were

conducted using similar but not identical methodologies, and each trial included detailed data about temperature decrements over time.

Figure 3-2 illustrates the dose-response between 10-15 mg/kg and 20-30 mg/kg. Mean temperature decrement over time is shown for acetaminophen doses of 10-15 mg/kg from 13 trials and 20-30 mg/kg from 3 trials. A reference line at 1ºC temperature decrement is shown.

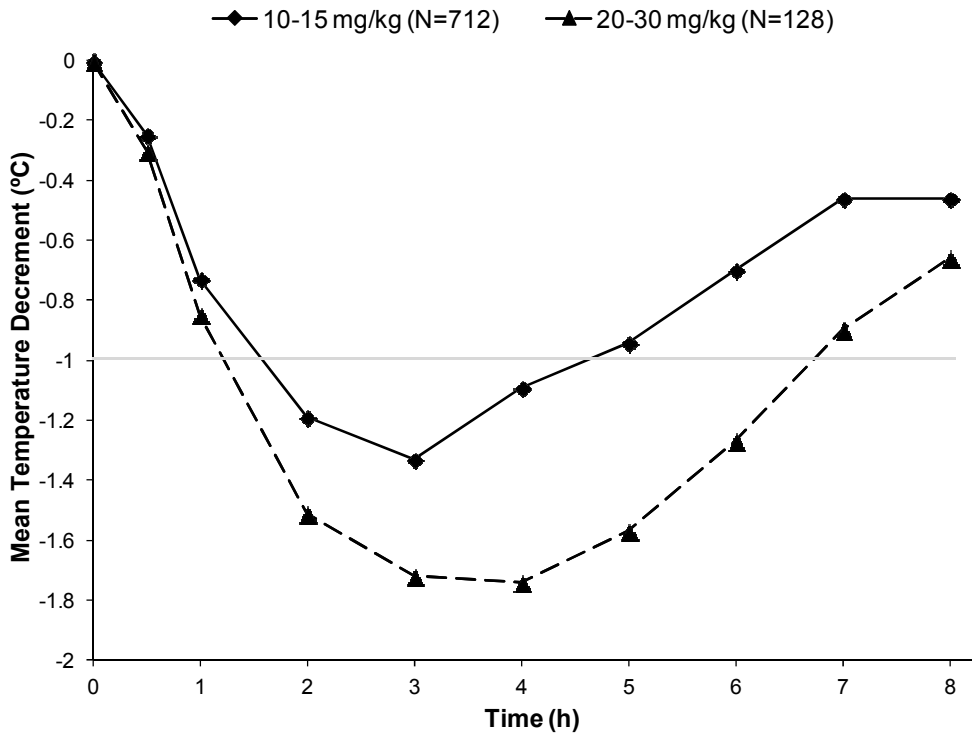


Figure 3-2. Cross-Study Comparison of Mean Temperature Decrement Over Time by Dose of Acetaminophen

Table 3-3 provides the weighted means for the maximum temperature decrement following acetaminophen administration (ΔTmax, °C), time to maximum temperature decrement (Tmax, hr), and, where possible, an estimate of duration of temperature decline greater than 1°C (ΔT>1°C, hr) in the 13 unpublished trials.

A dose of 10-15 mg/kg provided a clinically significant reduction in temperature reaching a maximum temperature decrement of 1.4°C between 2 to 3 hours following administration. The higher 20-30 mg/kg dose produced a greater maximum temperature decrement of 1.9°C, which was reached between 3 to 4 hours following administration, and had approximately twice the duration of temperature decrement greater than 1°C.

Table 3-3. Summary of Temperature Characteristics in Children by Dose of Acetaminophen (Unpublished McNeil Clinical Trials)

		Weighted Means			
Dose	N	Base Temp, ^{o}C	ΔT_{max}, ^{o}C	T_{max}, hr	$\Delta T > 1\ ^{o}$C, hr
10-15 mg/kg	712	39.25	1.4	2.85	2.53
20-30 mg/kg	128	39.27	1.9	3.67	5.20

Abbreviations: Base Temp = baseline temperature, ΔT_{max} = maximum temperature decrement, T_{max} = time to maximum temperature decrement, $\Delta T > 1^{o}$C = estimate of duration of temperature decline >1^{o}C

3.3.2 Dose Response Data From Published Clinical Trials

A comprehensive review of clinical trials published in the medical literature was undertaken to identify studies that evaluated the antipyretic efficacy of acetaminophen in children, either compared to placebo or to another antipyretic/analgesic agent and the doses used. Studies which had at least 1 oral acetaminophen-only treatment arm were identified. All studies were included whether they also included a placebo or active treatment controls, but only the data on acetaminophen is presented. Additional methodology surrounding these published clinical trials can be found in Section 3.9.

A total of 2185 children ranging from 2 months to 12 years of age were enrolled in the acetaminophen groups. Thirty trials included children less than 2 years of age, but the precise number of children in that age group could not be determined. Doses ranged from 6 to 30 mg/kg. Six studies used doses <10 mg/kg (average was approximately 8 mg/kg); 9 studies each used doses of 10 mg/kg, 13 studies used doses from >10 to <15 mg/kg, 11 studies used 15 mg/kg; and 2 used doses in the 20-30 mg/kg range. Although some studies reported use of a specific dose, it is likely that there was variability around each stated mg/kg dose given the available formulations, dosage devices, and lack of detailed dosing methodology.

Figure 3-3 shows temperature decrements for these 5 major dosing ranges by time period following drug administration using weighted averages. A reference line at 1ºC temperature decrement is shown. All doses provided some level of temperature decrement. Maximum temperature decrement generally was reached between 2 to 3 hours following administration. Higher doses produced increasingly greater maximum temperature decrements with a longer duration of temperature reduction. As can be seen, while all doses produced a maximum temperature decrement greater than 1ºC at some point in time, doses exceeding 10 mg/kg provided more prolonged and greater temperature decrements.

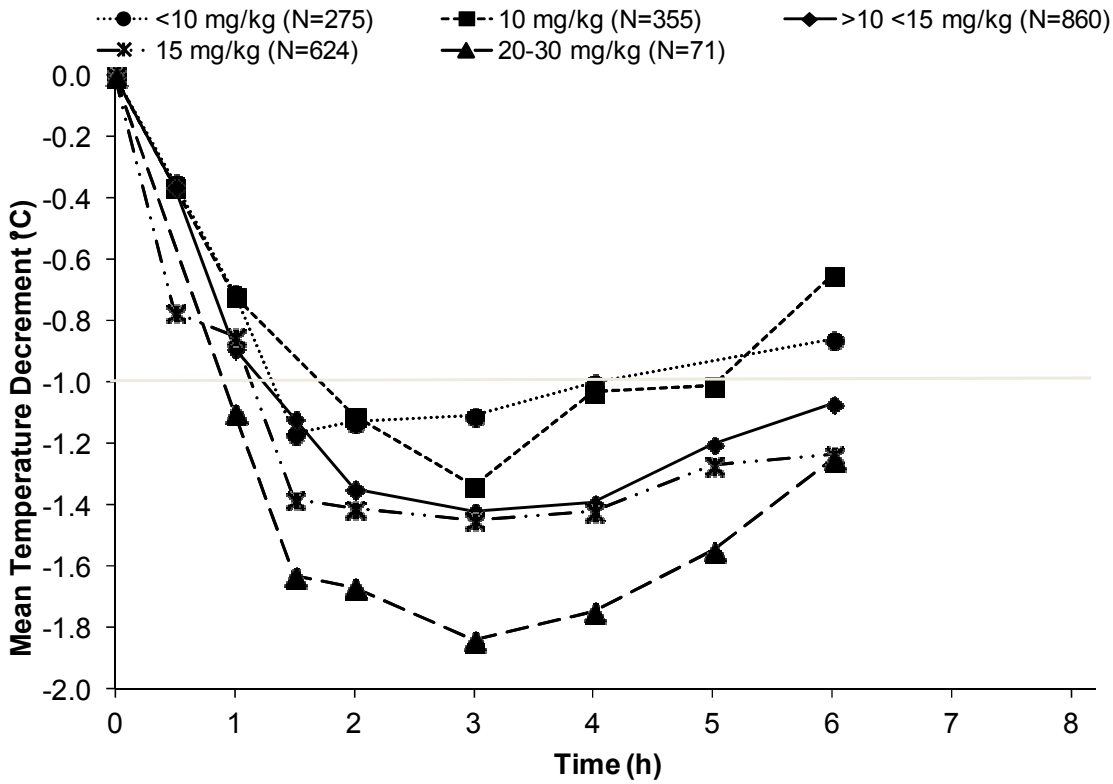


Figure 3-3. Published Clinical Trials by Mean Temperature Decrement vs Time Using Weighted Averages

Table 3-4 provides a summary of the weighted means for maximum temperature decrement following acetaminophen administration (ΔTmax, °C) and time to maximum temperature decrement (Tmax, hr) in the 39 published trials. An estimate of duration of temperature decline greater than 1°C (ΔT >1°C, hr) was not available for most trials and is not summarized here.

Table 3-4. Summary Temperature Characteristics in Children by Dose of Acetaminophen (39 Published Clinical Trials)

		Weighted Means			
Dose Group	N	Base Temp, ^{o}C	ΔT_{max}, ^{o}C	T_{max} hr	$\Delta T > 1\,^{o}$C, hr
6 to <10 mg/kg (Average 8 mg/kg)	275	38.74	1.33	2.51	--*
10 mg/kg	355	39.10	1.17	3.33	--*
>10 to <15 mg/kg	860	39.25	1.46	2.48	--*
15 mg/kg	624	39.07	1.54	2.99	--*
>15 to 30 mg/kg	71	39.25	1.90	2.82	--*

Abbreviations: Base Temp = baseline temperature, ΔT_{max} = maximum temperature decrement, T_{max} = time to maximum temperature decrement, $\Delta T > 1^{o}$C = estimate of duration of temperature decline >1^{o}C
* Not available from most trials

3.4 Summary of Additional Dose-Response Antipyretic Trials That Support Dosing in the Range of 10-15 mg/kg per Single Dose

In summary, antipyretic dose response data from clinical trials involving 3025 children 12 years of age or younger, 840 from unpublished McNeil clinical trials and 2185 from the published medical literature, confirm that doses in the range of 10-15 mg/kg provide a consistent, reproducible temperature decrement in febrile children.

In the McNeil trials, a dose of 10-15 mg/kg provided a clinically significant reduction in temperature reaching an average maximum temperature decrement of 1.4°C, between 2 to 3 hours following administration, with greater than 1ºC sustained for approximately 2 to 3 hours with clinically significant antipyretic effects lasting at least 4 hours following the initial dose. The 20-30 mg/kg dose produced a greater average maximum temperature decrement of 1.9°C, which was reached between 3 to 4 hours following administration, with greater than 1ºC sustained for at least 5 hours with a clinically significant antipyretic response lasting at least 6 hours following the initial dose. The higher dose produced greater decrements and provided a shorter period to reach at least 1.0°C decrement.

The published data show that for the doses ≤10 mg/kg, both the maximum temperature decrement and the duration of antipyresis greater than 1ºC were less than the effect shown with the 10-15 mg/kg dose. These data also confirm that the 10-15 mg/kg dose provides a clinically significant antipyretic effect lasting at least 4 hours following the initial dose.

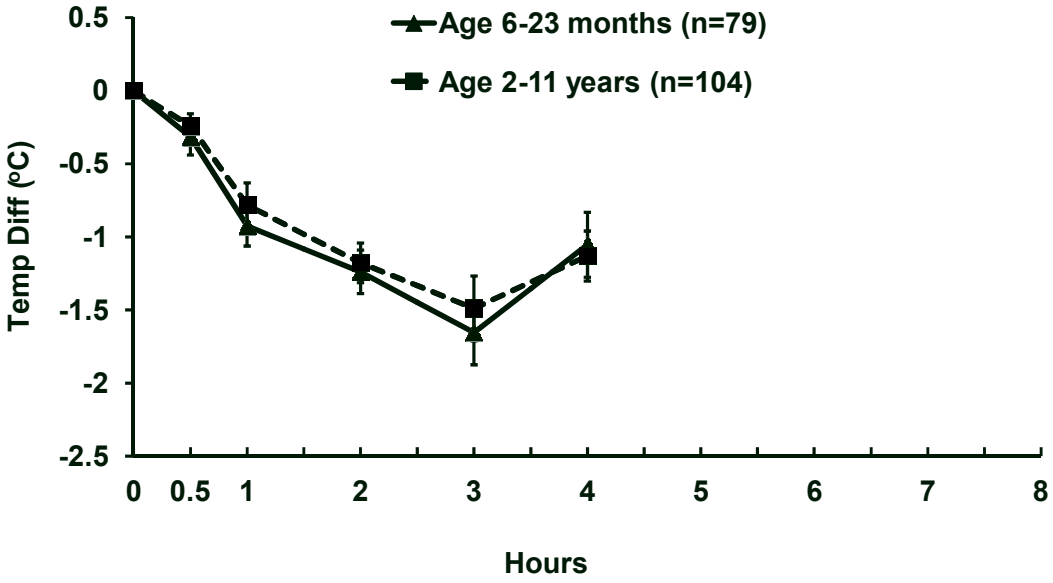
The findings of this analysis are particularly pertinent to the use of standardized dosing schedules first proposed over 27 years ago. Those age-related and weight-based schedules consistently maintain dosing of acetaminophen in the 10-15 mg/kg per dose range and for that specific dosing range the data show a remarkable consistency of antipyretic response.

3.5 Evaluation of Dose Response Data Shows That the Antipyretic Efficacy of 10-15 mg/kg Single Dose is Similar in Children Less Than 2 Years of Age Compared with Children 2 to 11 Years of Age

In order to better understand the antipyretic response in children less than 2 years of age compared to older children, we have analyzed a subset of McNeil studies. Four studies, 2 single dose (86-639, 82-222) and 2 multiple dose (80-220, 86-640), were identified with available data which enrolled subjects both less than 2 years of age and 2 years of age and older. A description of each individual study is included in Table 3-5. In the 2 multiple dose studies, redosing was allowed at 4 hours.

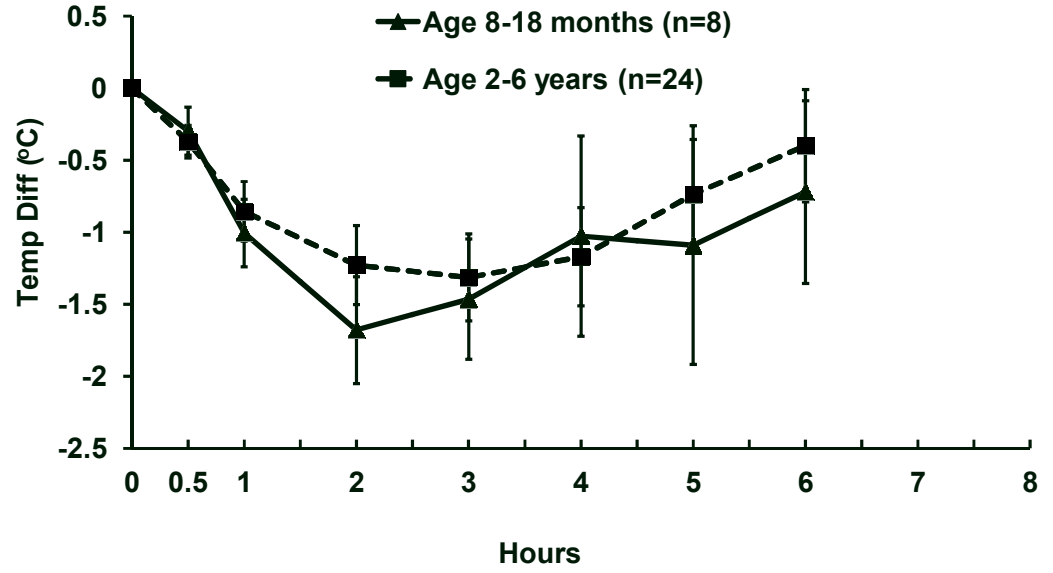
Mean temperature change from baseline and 95% confidence intervals, in degrees Celsius, are shown for 2 groups: those less than 2 years of age and those 2 years of age and older, up to 11 years of age. A negative change from baseline indicates a decrease in temperature from baseline. Each subject is weighted equally in the average.

Figure 3-4 presents the mean change from baseline up to 4 hours where all 4 studies have been combined. The time up to 4 hours was used because this represented the single dose period for all studies. The mean temperature change from baseline is presented for each study individually in Figure 3-5 and Figure 3-6 for the 2 single dose studies and in Figure 3-7 and Figure 3-8 for the multiple dose studies. In Study 86-639, subjects were monitored for 6 hours (Figure 3-5). In Study 82-222, subjects were monitored for 8 hours (Figure 3-6). In Study 80-220, all subjects were redosed at 4 hours so the figure shows data for 2 dosing periods (Figure 3-7). In Study 86-640, subjects were allowed, but not required to dose after 4 hours; therefore, mean temperatures are shown only up to 4 hours (Figure 3-8).



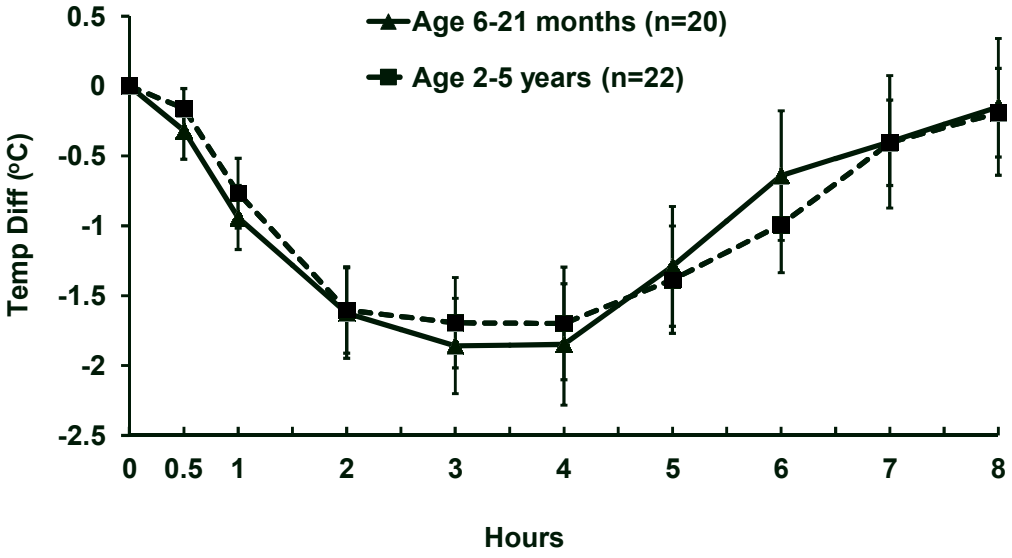
Studies 80-220, 82-222, 86-639 & 86-640

Figure 3-4. Reduction in Mean Body Temperature (95% CI) with Acetaminophen 10-15 mg/kg by Age Group for Studies 80-220, 82-222, 86-639, 86-640



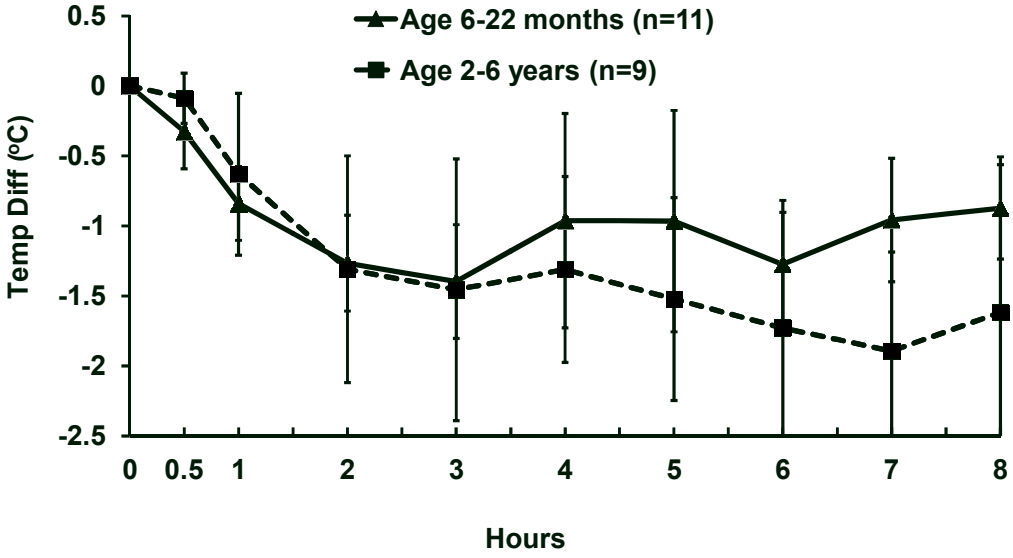
Study 86-639

Figure 3-5. Reduction in Mean Body Temperature (95% CI) with Acetaminophen 10-15 mg/kg by Age Group for Study 86-639



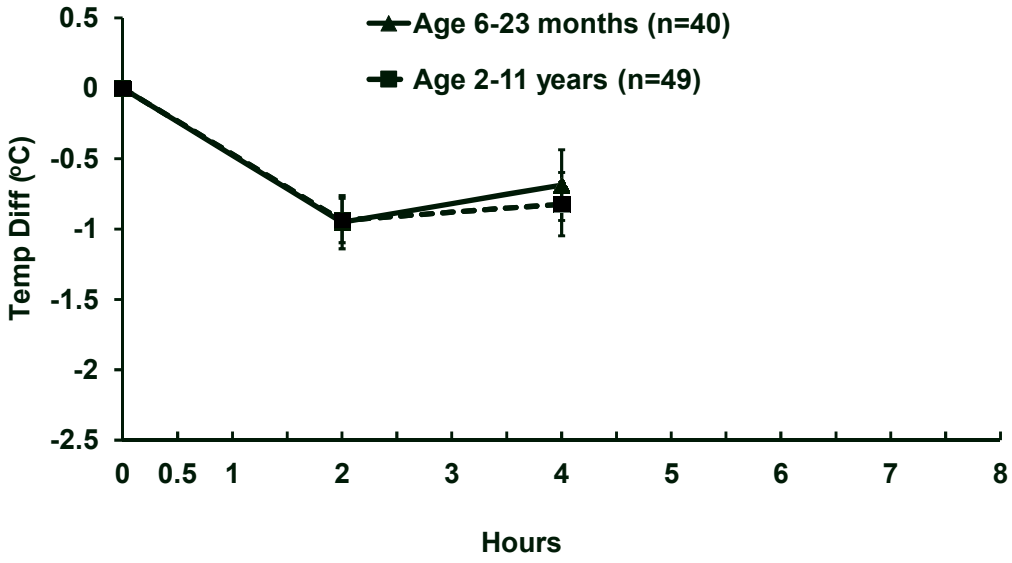
Study 82-222

Figure 3-6. Reduction in Mean Body Temperature (95% CI) with Acetaminophen 10-15 mg/kg by Age for Study 82-222



Study 80-220

Figure 3-7. Reduction in Mean Body Temperature (95% CI) with Acetaminophen 10-15 mg/kg by Age Group for Study 80-220



Study 86-640

Figure 3-8. Reduction in Mean Body Temperature (95% CI) with Acetaminophen 10-15 mg/kg by Age Group for Study 86-640

When dosed by weight using schedules to achieve doses in the 10-15 mg/kg dosing range, the antipyretic response with both single doses and multiple doses is very similar between children less than 2 years of age and those who were 2 years of age and older. When there are observed differences in temperature reduction between age groups, there is no consistent pattern of temperature reduction with regard to age group across studies.

3.6 Analgesic Efficacy of Acetaminophen 10-15 mg/kg in Children

Acetaminophen at 10-15 mg/kg has been shown to be effective in children in a variety of analgesic models.

Clinical trials involving post-immunization pain [8] and pain following otolaryngology procedures such as myringotomy and tube insertion [9, 10, 11] have demonstrated the analgesic effectiveness in children less than 2 years of age as well as children 2 to 11 years of age. In addition, acetaminophen has been shown to be effective for pain related to heel stick [12] and circumcision [13] in children less than 2 years of age and for acute limb fractures [14], sore throat pain [15, 16], migraine [17, 18], and isolated soft tissue injuries [19] in children 2 to 11 years of age.

It should be noted that pharmacokinetic-pharmacodynamic modeling suggests that doses of acetaminophen required for effective analgesia may be higher than those

required for effective antipyresis [20]. Mean EC50[2] concentrations ranging from 4.63 to 7.09 µg/mL have been reported for antipyresis [21, 22] compared to an EC50 of 9.98 µg/mL for analgesia [23]. For some children in pain, higher doses within the 10-15 mg/kg range may be required to provide adequate analgesia. From an efficacy perspective, weight-based dosing may be even more important than age-related dosing when treating pain compared with fever.

3.7 Conclusions

- Extensive antipyretic efficacy data from clinical trials support the single OTC dose of acetaminophen of 10-15 mg/kg for children.

- Clinical trials have confirmed the antipyretic efficacy of the 10-15 mg/kg dose in children 6 to 23 months of age. In clinical trials, the course of fever and its response to the same mg/kg doses of acetaminophen is similar in children 6 to 23 months of age and children 2 to 11 years of age.

- Acetaminophen 10-15 mg/kg has also been shown to be an effective analgesic in children 6 to 23 months of age.

[2] EC50 is the plasma concentration required to obtain 50% of the maximum effect. Acetaminophen concentration-response and EC50 in children 6 to 23 months is addressed in Section 4.

3.8 Supportive Methodology for the Dose Response Data From Unpublished McNeil Consumer Healthcare Clinical Trials

Thirteen unpublished McNeil clinical trials were identified which evaluated the use of acetaminophen in fever reduction [24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]. Five trials included children less than 2 years of age, while all 13 included children 2 years of age and older. Two basic dosing regimens were used in these trials: standard doses in the 10-15 mg/kg range (12.5 mg/kg average dose) or double-standard doses in the 20-30 mg/kg range (25 mg/kg average dose). Three of these studies reported data on both standard and double-standard doses. Three studies reported data on standard doses and a double-standard non-marketed extended release acetaminophen product (data from the extended release is not included here). Seven trials included comparisons against other non-acetaminophen antipyretics. None were placebo-controlled trials.

In the McNeil trials some temperatures were reported in Fahrenheit and others in Celsius. For comparative analysis all temperatures were converted to Celsius. In some of the studies an actual maximum temperature decrement (ΔTmax) was calculated as an average of the maximum decrements for each individual subject. When this was not reported, the maximum temperature decrement among the average temperature decrements by time period following drug administration was used as the ΔTmax. Statistically, calculated ΔTmax values of the average of the maximum decrements for each subject are somewhat greater than any individual average ΔTmax by time period. Thus, the overall average ΔTmax for any given dose, which includes both types of calculations, may be slightly understated.

3.9 Supportive Methodology for the Dose Response Data From Published Clinical Trials

Literature searches were conducted using the PubMed database, with search terms of “acetaminophen” or “paracetamol” in the title or abstract. The search was limited to the following criteria: randomized controlled studies using oral routes of administration conducted in pediatric patients less than 12 years of age; publications in the English language or translated. We reviewed the period from 1982 through 31 October 2010. To be included in the dosing efficacy analysis, the study contained sufficient dosing detail to verify doses used, in mg/kg and dosing frequency for multiple dose trials. Articles were excluded if the study did not report any efficacy measurements or if acetaminophen was administered only via non-oral routes. In some of the published trials actual values for temperature were not reported, so estimates were made from figures provided in the paper.

The literature search identified 39 clinical trials that met our selection criteria, specifically containing single dose data, which were included in the review [3, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74]. Each of the listed published studies evaluated antipyretic efficacy of acetaminophen using standard antipyretic measurement techniques. Published studies were not consistent in times of measurement and had a variety of doses of acetaminophen used, but each was found to contain some data about patterns of temperature decrement following drug administration. The 39 published studies included 37 studies that investigated 1 dose of acetaminophen and 2 studies that investigated 2 doses of acetaminophen. Multiple dose studies evaluating antipyretic efficacy of acetaminophen, which contained data on response to the initial dose of acetaminophen were included. Most multiple dose trials did not collect detailed initial dose response, so their data could not be used to assess actual antipyretic efficacy.

3.10 Supportive Table

Table 3-5. Study Methodology For the 4 McNeil Studies Comparing Children Less Than 2 Years of Age With Children 2 to 11 Years of Age

Study	Methodology
Study 80-220	This was a double-blind, parallel, multicenter, multiple dose study comparing acetaminophen 10-15 mg/kg every 4 h and acetaminophen 24-30 mg/kg every 8 h for up to 3 days in 48 children >6 m to <6 y with a rectal temperature ≥101ºF.
Study 82-222	This was a double-blind, parallel, multicenter, single dose study comparing acetaminophen 10-15 mg/kg with acetaminophen 20-30 mg/kg in 88 children >6 m to <6 y with a rectal temperature ≥102ºF.
Study 86-639	This was a randomized, open-label, parallel, multicenter, single-dose study comparing acetaminophen 12 mg/kg to ibuprofen 3 mg/kg, ibuprofen 6 mg/kg, and ibuprofen 9 mg/kg in 129 children 0.7 y-6 y of age. Children 6 m-3 y with rectal temperatures ≥102.0°F and ≤104.9°F and children 4-6 y with oral temperatures ≥101.0°F and ≤103.9°F were included.
Study 86-640	This was a randomized, double-blind, parallel, multicenter, multiple dose study comparing acetaminophen 10-15 mg/kg every 4 h and ibuprofen 5-7 mg/kg every 4 h for up to 4 days in 409 children 0.5 y-11 y of age. Children 6 m-3 y with a rectal temperature ≥102°F and ≤104.9°F and children 4-11 y with an oral temperature ≥101°F and ≤103.9°F.

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SECTION 4

PHARMACOKINETIC BASIS FOR PEDIATRIC ACETAMINOPHEN DOSES

TABLE OF CONTENTS

4 PHARMACOKINETIC BASIS FOR PEDIATRIC ACETAMINOPHEN DOSES

4.1 McNeil's Position

Acetaminophen 10-15 mg/kg as a single dose has demonstrated efficacy, and is widely used and accepted by health care professionals for children 6 months to 11 years of age. McNeil designed its weight-based and age-related OTC dosing instructions with the goal of consistently producing a dose within the 10-15 mg/kg range across the pediatric population [1].

The purpose of Section 4 is to summarize pediatric pharmacokinetic data and an integrated analysis across studies that bridge acetaminophen exposure[1] in children ages 6-23 months to that in children ages 2-11 years, and to evaluate McNeil's proposed OTC dosing chart through modeling and simulations. The fundamental relationship that connects exposure, administered dose, and drug clearance (rate of removal) provides the means by which to explore the effects of maturation and body size on the selection of appropriate pediatric doses. Additional data on the antipyretic response to acetaminophen concentrations for children ages 6 months to 11 years further supports the proposed weight-based and age-related OTC dosing charts.

4.2 Key Points

- Acetaminophen Clearance: Effects of maturation of metabolic pathways and body size on acetaminophen clearance have been widely studied.
    - Children ages 6-23 months metabolize acetaminophen efficiently by sulfation as glucuronidation matures.
    - Two acetaminophen population pharmacokinetic models based on extensive data from neonates through adults have described the effects of maturation and body size on acetaminophen clearance, and thus, can be used to reliably predict exposure from various pediatric doses.
- Acetaminophen Exposure: An integrated analysis of acetaminophen exposure across multiple McNeil-sponsored pediatric and adult studies demonstrated the following:
    - The effective 10-15 mg/kg dose provided children ages 6-23 months with comparable exposure as that in children ages 2-11 years.

[1] Exposure is expressed as area under the concentration-time curve (AUC).

  - Acetaminophen exposure increased only slightly with age from 6 months to 50 years, and would not be expected to be clinically important.

- Multiple-Dose Exposure: Acetaminophen plasma concentrations reach steady state within 10 to 15 hours of repeated dosing without progressively accumulating in neonates, infants, children, and adults. This was also demonstrated with McNeil study data in children from 6 months to 6 years of age.
- Acetaminophen Concentration-Response: Published and unpublished pharmacokinetic-pharmacodynamic studies of acetaminophen in children and adults support the following:
  - Concentrations from 5 to 7 µg/mL are needed for 50% of maximum fever reduction (EC50), which are generally lower than concentrations from 10 to 17 µg/mL needed for 50% of maximum pain relief.
  - An integrated analysis of acetaminophen concentration-response data across multiple McNeil-sponsored pediatric fever studies showed that the EC50 for children ages 6-23 months is similar to children 2-11 years.
- Evaluation of Pediatric Doses by Simulations: A model that describes acetaminophen exposure and account for age and body size effects on clearance and McNeil pediatric data were used to evaluate the proposed OTC doses for children 6-23 months. The cohort of children ages 2-11 y provided reference exposure range. Simulations showed that both the proposed weight-based and age-related charts provide appropriate doses for children ages 6-23 months by maintaining acetaminophen exposure close to the reference range.

4.3 What is Known About Metabolism and Pharmacokinetics in Children?

4.3.1 Maturation Effects on Acetaminophen Metabolism

Acetaminophen metabolism has been widely studied across populations from neonates through adults, and Table 4-1 lists the main developmental differences for infants. Only about 2% to 5% of an administered dose is excreted unchanged in urine. Results from published studies have increased our current understanding of maturation effects on how efficiently acetaminophen is removed or cleared from the body. With this knowledge, pediatric doses can be evaluated for any measurable differences in clearance due to metabolic maturation after adjusting for body size.

Acetaminophen is mainly eliminated by direct Phase II conjugation to form inert glucuronide and sulfate metabolites in children and adults [2,3,4]. Conjugation metabolism eliminates about 80% to 85% of a dose. One difference between younger children and adults is that the ratio of glucuronide to sulfate produced is higher in adults [5,6].

Studies have shown that, although glucuronidation is not fully mature in all children until about three years of age, sulfation is compensatory and efficient, becoming the primary metabolic pathway for acetaminophen [7,8]. Furthermore, a metabolism study with neonates found enhanced glucuronidation with repeat acetaminophen dosing [9], a finding that has been reported in adults [10]. Enhanced glucuronidation represents a useful, protective metabolic pathway, because it moves more acetaminophen away from oxidative pathways.

Acetaminophen is metabolized by Phase 1 oxidation to a lesser extent, where oxidation eliminates about 10% to 15% of a dose [11]. One study showed no differences in cytochrome P4502A6 protein levels between adults and infants ≥ 1 year, suggesting its development is complete by the first year of life [12]. By contrast, cytochrome P4502E1 enzyme expression is lower in infants than during adulthood, especially before approximately three months after birth, thereby reducing the formation of the highly reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI), from acetaminophen [13]. This highly reactive intermediate is conjugated with glutathione to form nontoxic thiol metabolites that are excreted in urine.

For children 6-23 months, maturation of the oxidative pathways would not result in measurable differences in acetaminophen clearance compared with children 2-11 years because these are minor pathways for elimination. The effect of glucuronidation maturation on acetaminophen clearance, and hence on selection of pediatric doses, has been described by population pharmacokinetic models (Refer to Section 4.3.2.2).

Table 4-1. Maturation of Acetaminophen Metabolic Pathways

Enzymes	Cofactors	Metabolites	Developmental Pattern	Citations
Phase II Conjugation (Major)				
UGT1A6 UGT1A9	Glycuronic acid	Glucuronide	Infants have 50% adult activity by 6 mo; maturation reached by 3 y	[7,8]
SULT1A1 SULT1A3	PAPS	Sulfate	Activity is at relatively constant levels from gestation though adulthood	[4]
Phase I Oxidation (Minor)				
CYP2A6		Catechols	Maturation reached by 1 y	[12]
CYP2E1	GST/Glutathione	Thiols	Infants up to 3 mo after birth have lower activity than adults	[13]

Key: GST = Glutathione S-Transferase; PAPS = 3'-Phosphoadenosine-5'Phosphosulfate

4.3.2 Classical and Population Pharmacokinetics from Neonates to Adolescents

4.3.2.1 Single-Dose Pharmacokinetics Studies

Acetaminophen pharmacokinetics after administration of a single dose has been evaluated in all pediatric populations from preterm neonates through adolescents [5,6,14,15]. Data are available with oral, rectal, and intravenous formulations. However, children 6-23 months of age are often enrolled in pharmacokinetic studies with children 2-11 years of age, and hence, specific information on this younger cohort after oral dosing is limited [16,17]. Most studies have a classical design in which acetaminophen pharmacokinetics are estimated for individual subjects in the study population after collecting several blood samples per subject. Therefore, they do not inform on population variability of the estimates.

4.3.2.2 Published Population Pharmacokinetic Models

Anderson and colleagues have developed two acetaminophen population pharmacokinetic models. The aim of the first model published in 2000 was to describe size and age (maturation) changes in the pharmacokinetics of acetaminophen in neonates, infants, and children [18]. The pooled analysis included 1653 concentrations from 221 children, ages one day to 15 years (mean, 20 months), and children were administered oral liquid or rectal suppositories. The population estimate of oral clearance, CLstd, was 13.0 L/h/70kg with a between-subject variance of 41%.

The second model published in 2009 expanded the population range from premature neonates through young adults, and also had data for an intravenous formulation of acetaminophen [19]. The pooled analysis included 3049 concentrations from 509 subjects.

With inclusion of premature neonates, the use of postmenstrual age provided a better fit of the model to data. The population estimate of clearance, CLstd, was 16.2 L/h/70kg with a between-subject variance of 45%.

Both Anderson population pharmacokinetic models show that acetaminophen clearance depends on body size.

- Choice of the size model for body size has a significant role in estimating pediatric pharmacokinetic parameters and drug doses [18].
- Body weight has been used most commonly to scale for size in pediatric dosing rules, despite the nonlinear relationship between weight and dose. The weight-based models tend to give the best estimates of infant doses based on precision and bias [20]. However, they tend to underestimate doses for certain ages across the entire pediatric population, depending on the selected age range for each dose division.
- The allometric size model of body weight to the ¾ th power was selected in both acetaminophen population pharmacokinetic models because it best represented the effect of body size on clearance [21].

These population models can be used to evaluate pediatric dosing rules for acetaminophen, because exposure (AUC) is related to dose and clearance. For example, the Anderson 2000 model showed that acetaminophen clearance increases exponentially from birth with a half-life of 3.25 months, and predicted clearance in a 6-month-old child is 80% compared with that of a 2-year-old [18]. This model can be used to predict whether the 80-mg dose for a 6-month-old child, which is 50% of the 160-mg dose for a 2-year-old child, would achieve similar acetaminophen exposure.

4.4 Comparison of Acetaminophen Exposure at the 10-15 mg/kg Dose for Children, Ages 6-23 Months and 2-11 Years

Acetaminophen exposure, measured as area under the concentration-time curve extrapolated to infinity (AUC_{INF}) is of primary importance in evaluating pediatric data, because it is related to the administered dose and its bioavailability. As discussed previously, AUC_{INF} is also related to oral clearance or the rate of drug removal.

To evaluate whether the 10-15 mg/kg dose provides acetaminophen exposure for children ages 6-23 months that is similar to children ages 2-11 years, an integrated analysis of pharmacokinetic data across multiple pediatric and adult studies was completed. The methods and results are summarized in this section.

4.4.1 Integrated Analysis of Pharmacokinetic Data Across Multiple Studies

Pediatric pharmacokinetic data were pooled from five unpublished studies sponsored by McNeil [22,23,24,25,26] and from one by a pediatric clinical investigator (personal communication) [27]. Five studies were conducted with febrile children and one study [27] with healthy children who received acetaminophen during immunization. Either one or two 10-15 mg/kg doses or one 20-30 mg/kg dose of acetaminophen was administered as an oral liquid. Per protocol, the children were dosed by weight. Altogether the studies enrolled 137 children ranging from 3 months to 11 years of age, from which 113 children had evaluable pharmacokinetics using either noncompartmental or one-compartment modeling methods. Five children were not included in the final dataset (N=108): three were ages 3-4 months, and two were administered doses far outside 10-15 mg/kg and 20-30 mg/kg.

Pharmacokinetic data from three unpublished studies in healthy adults sponsored by McNeil were pooled for the integrated analysis [28,29,30]. These studies were selected because subjects were administered an oral liquid and the 960-mg acetaminophen dose. This adult dose is consistent with the 40- and 80-mg dose increments on the children's weight-based dosing charts, and it similarly provides mg/kg doses within the 10-15 mg/kg range. Table 4-2 summarizes the dataset by age and dose groups.

Table 4-2. Integrated Pharmacokinetic Dataset for Acetaminophen Oral Liquid

Age Group	Total N	Gender M/F (nr)	Race A/B/W/M (nr)	10-15 mg/kg	20-30 mg/kg
Children 6-23 months	49	28/14 (7)	0/4/3/1 (41)	24 [a]	25
Children 2-11 years	59	27/20 (12)	0/4/21/0 (34)	43	16
Adults 18-50 years	60	100/0 (0)	2/6/52/0 (0)	60	—

a: Includes two children who were 5.5 and 5.8 mo of age
Key: A – Asian, B – Black, F – female, M (gender) - male, M (race) – mixed, W – white, nr – not reported.

4.4.2 Statistical Methods

In addition to total acetaminophen exposure, AUC_{INF}, maximum exposure (C_{MAX}) was included as a secondary metric, because it provides supportive information. For the primary analysis of exposure among age groups, individual exposure values for children who received the 20-30 mg/kg dose were standardized to the 10-15 mg/kg dose by dividing by 2 (SAUC and SC_{MAX}). These data were pooled with single-dose estimates of AUC_{INF1} and C_{MAX1} for children and adults who received the 10-15 mg/kg dose. The standardization of dose is appropriate because acetaminophen follows linear pharmacokinetics at low doses.

The standardized exposure parameters for the 10-15 mg/kg dose, SAUC and SC_{MAX}, were log-transformed before the statistical analysis. A linear mixed model was fitted with study as a random effect and age group (6-23 months, 2-11 years, adults) as a fixed effect. This model was used to calculate the geometric mean ratio and 90% confidence interval (CI), comparing exposures for children 6-23 months with exposures for children 2-11 years and adults as reference groups. In addition, exposures for children 2-11 years were compared with those in adults. The equivalence boundary was defined as 80% to 125% for comparisons of the geometric SAUC and SC_{MAX} ratios for children ages 6-23 months relative to children ages 2-11 years as the reference group.

To further examine the effect of age on acetaminophen exposure, a linear regression of the log of SAUC on age was performed for children ages 6 months to 11 years plus adults, and also for children ages 6 months to 11 years. The slope and its 95% confidence interval are presented for each regression, along with the significance test of the null hypothesis that the slope is equal to zero.

4.4.3 Results

In 6 of 9 pooled studies, children and adults received two 10-15 mg/kg doses of an acetaminophen oral liquid four hours apart, and the mean pharmacokinetic profiles are displayed in Figure 4-1 by age group and study. Overall these data illustrate that the concentration-time curves were similar among adults and both pediatric age groups. For the single 20-30 mg/kg dose, individual data across four pediatric studies were pooled, and the mean pharmacokinetic profiles for children 6-23 months and 2-11 years are displayed in Figure 4-2. These concentration-time curves at the higher dose were also similar between age groups.

Figure 4-1. Mean Pharmacokinetic Profiles of Two 10-15 mg/kg Doses of Acetaminophen Oral Liquid by Age Group and Study

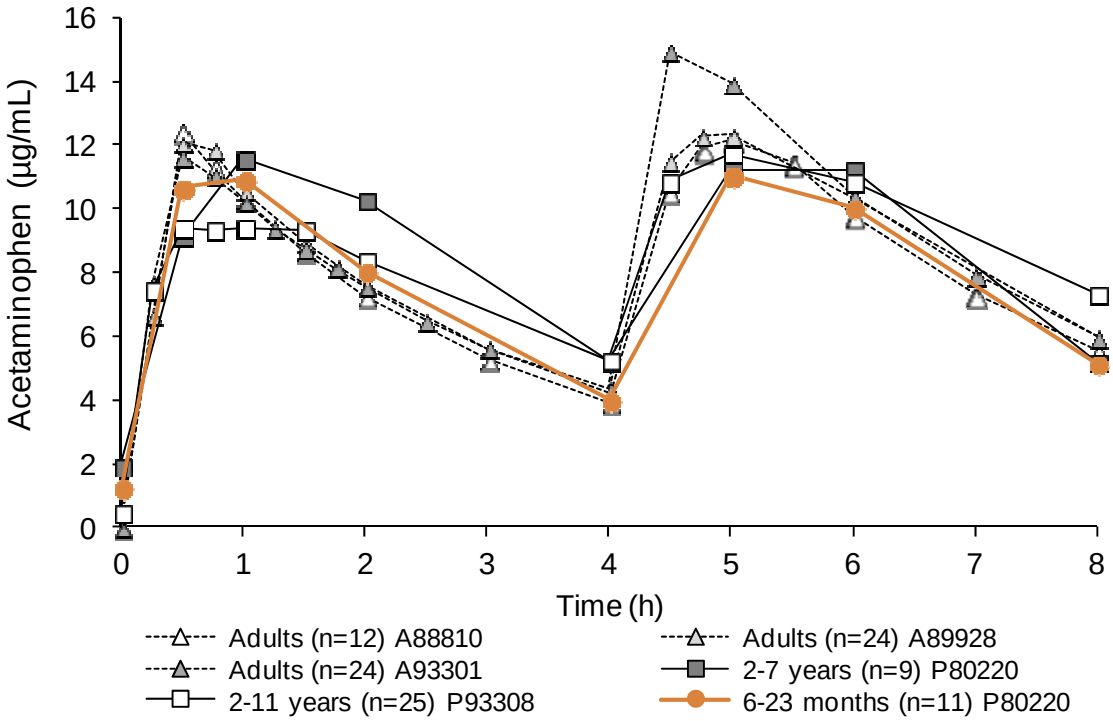
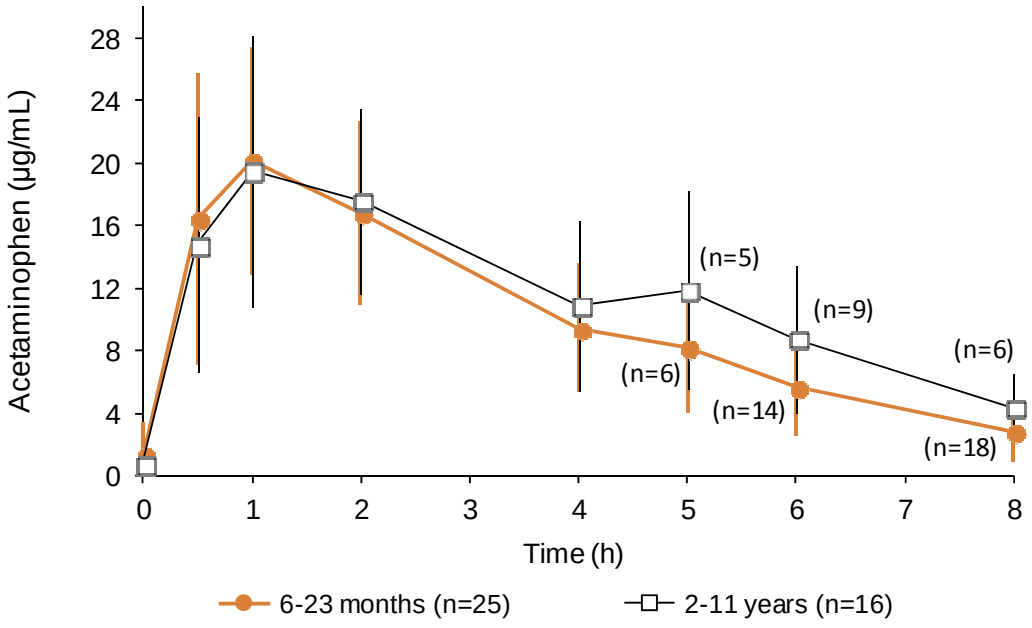


Figure 4-2. Mean (sd) Pharmacokinetic Profiles of One 20-30 mg/kg Dose of Acetaminophen Oral Liquid by Age Group and Pooled Across Studies



4.4.3.1 Comparison of Acetaminophen Exposure Among Age Groups

The exposure data for the 20-30 mg/kg dose were standardized to the 10-15 mg/kg dose by dividing by 2 so that they could be further pooled for the integrated analysis of exposure among age groups. Summary statistics for the exposure parameters are presented in Table 4-3 by age and dose groups for one dose and the standardized 10-15 mg/kg dose, and by age group for the pooled standardized dose (shaded section).

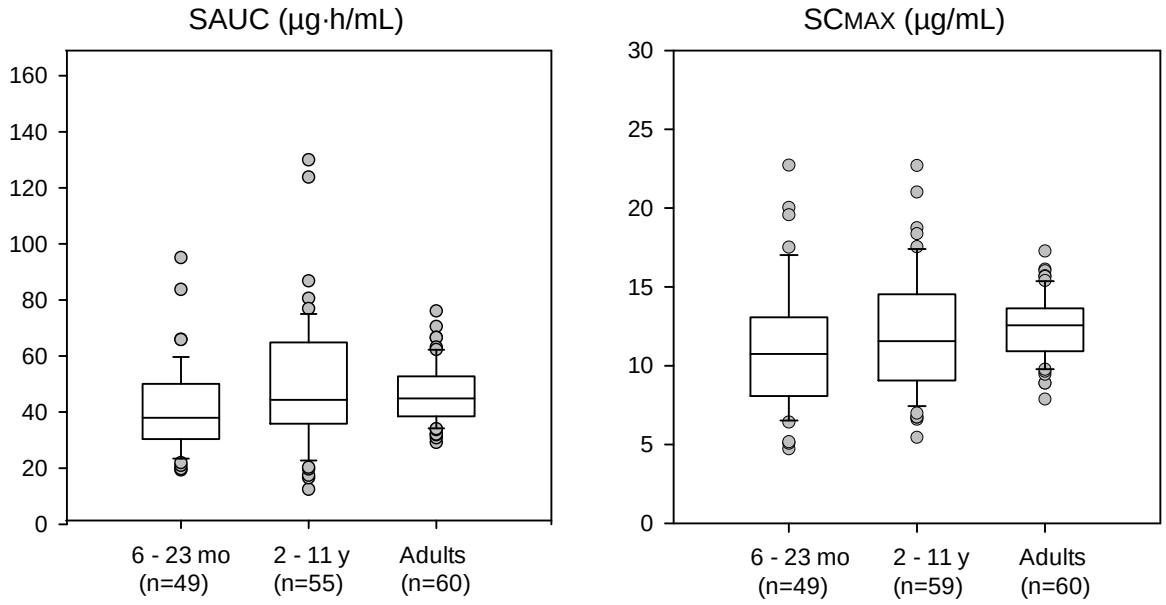
Box plots for SAUC and SC_{MAX} by age group that include median and the 25th and 75th percentiles are shown in Figure 4-3. These plots show that acetaminophen exposures for children 6-23 months and 2-11 years are comparable, although the variability was higher for children 2-11 years. There appears to be slightly higher median exposures and less variability for the adult group.

Table 4-3. Summary Statistics[a] of Acetaminophen Exposure[b] by Age and Dose Group

Age Group	Dose Group	Total N	AUC_{INF1} (µg·h/mL)	C_{MAX1} (µg/mL)	SAUC (µg·h/mL)	SC_{MAX} (µg/mL)
Children 6-23 mo	10 -15 mg/kg	24	35.4 35% [35.93]	10.5 35% [10.64]	35.4 35% [35.93]	10.5 35% [10.64]
Children 6-23 mo	20 -30 mg/kg	25	84.2 37% [86.37]	20.9 39% [21.50]	42.1 37% [43.18]	10.5 39% [10.75]
Children 2-11 y	10 -15 mg/kg	43	45.5[c] 46% [44.20]	11.5 35% [11.87]	45.5[c] 46% [44.20]	11.5 35% [11.87]
Children 2-11 y	20 -30 mg/kg	16	92.0 60% [104.7]	22.1 24% [21.95]	46.0 60% [52.36]	11.0 24% [10.98]
Children 6-23 mo	10 -15 mg/kg	49	—	—	38.7 37% [37.96]	10.5 37% [10.75]
Children 2-11 y	10 -15 mg/kg	59	—	—	45.7[c] 50% [44.41]	11.4 33% [11.56]
Adults 18-50 y	10 -15 mg/kg	60	45.4 22% [44.90]	12.4 17% [12.57]	45.4 22% [44.90]	12.4 17% [12.57]

a: Described by geometric mean, %CV of geometric mean, [median]
b: AUC_{INF1} and C_{MAX1} are exposures for one dose, SAUC and SC_{MAX} are exposures standardized to the 10-15 mg/kg dose.
c: AUC_{INF1} and SAUC could not be estimated for four children.

Figure 4-3. Box Plot Comparison of Acetaminophen Exposure by Age Group Standardized to the 10-15 mg/kg Dose



Results from the statistical comparison of standardized acetaminophen exposures by age group are listed in Table 4-4. Both SAUC and SCMAX for children ages 6-23 months in this pooled analysis were equivalent to exposures in children ages 2-11 years, as the 90% confidence intervals were contained within the 80% to 120% boundaries. Only SCMAX for children ages 2-11 years were within the equivalence boundaries when compared with exposure in adults. The remaining exposure estimates for the children's groups were not within the equivalence boundaries, as they were slightly lower. These results are consistent with the rank order of boxes in Figure 4-3.

Table 4-4. Statistical Comparison of Acetaminophen Exposure by Age Group Standardized to the 10-15 mg/kg Dose

	SAUC		SCMAX	
Comparison	Ratio of Geomeans	90% Confidence Intervals	Ratio of Geomeans	90% Confidence Intervals
Children 6-23 mo vs 2-11 y	91.3	80.5 to 103.6	91.5	83.0 to 100.9
Children 6-23 mo vs Adults	89.4	67.4 to 118.7	83.6	74.9 to 93.2
Children 2-11 y vs Adults	97.9	73.9 to 129.8	91.3	82.1 to 101.5

a: The linear mixed model was used to construct the two-sided 90% confidence limits.

4.4.3.2 Log-Linear Regression Analysis by Age

Log-linear regression is another manner by which to evaluate whether acetaminophen exposure was influenced by age over the specific age range of interest in this integrated analysis. Statistical results of the log-linear regression analysis of standardized acetaminophen exposure versus age are shown in Table 4-5 on the natural logarithm scale: Ln (SAUC) = Slope x Age (mo) + Intercept. The scatter plot of SAUC for children ages 6-23 months (N=49) and 2-11 y (N=55), and adults (N=60) with the regression line is shown in Figure 4-4.

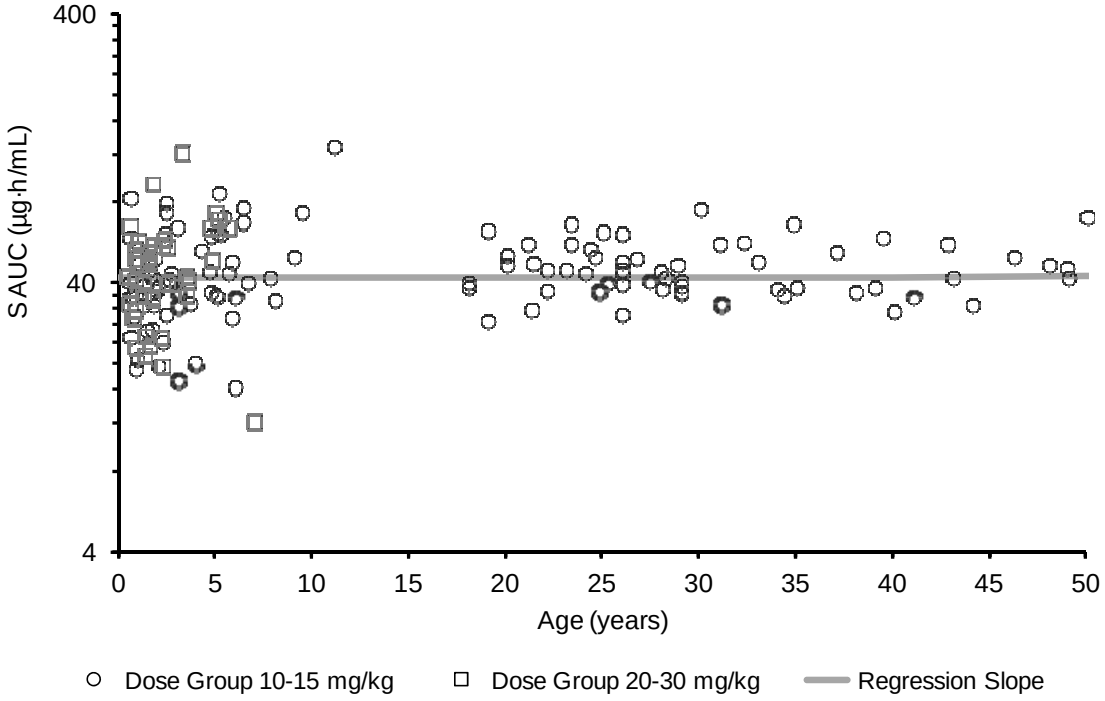
Both models had a positive slope, although the slope for the full range of ages that includes adults was not statistically significant. In addition, both models are consistent with medians and geometric means of acetaminophen exposure for the children ages 6-23 months being slightly lower than those for the older age groups. Overall, these results indicate that acetaminophen exposure for the 10-15 mg/kg oral dose increased only slightly with age from 5.5 months to 50 years, and would not be expected to be clinically important.

These results are only informative regarding exposure for children from 5.5 months of age through adults 50 years of age, because no exposure data were available in the pooled pharmacokinetic dataset beyond these age limits. It is well understood that acetaminophen exposures in neonates and infants ≤ 29 days would not be predicted by a log-linear regression model with age. Instead, actual AUC values for the same mg/kg dose would be higher near the intercept, where age is approximately zero, due to maturation effects on acetaminophen clearance [18,19].

Table 4-5. Regression results of Standardized Acetaminophen Exposure by Age Group

Age Group	N	Age Range	Intercept	Slope [95% CI] x 10^{-4}	p Value
Children and Adults	164	5.5 to 600 mo (0.46 to 50 y)	3.730	2.58 [-0.734 to 5.89]	0.1262
Children	104	5.5 to 133 mo (0.46 to 11 y)	3.614	37.0 [7.05 to 66.9]	0.0159

Figure 4-4. Scatter Plot of Standardized Acetaminophen Exposure on the Log-Scale as a Function of Age (5.5 Months to 50 years)



4.4.3.3 Conclusions from the Integrated Analysis of Exposure

The integrated analysis of acetaminophen exposure across multiple McNeil-sponsored pediatric and adult studies demonstrated the following:

- The effective 10-15 mg/kg dose provided children ages 6-23 months with comparable exposure as that in children ages 2-11 years, as the ratio of geometric means for both SAUC and SC_{MAX} fell within the equivalence boundaries.
- Acetaminophen exposure increased only slightly with age from 5.5 months to 50 years, and would not be expected to be clinically important.

4.5 Acetaminophen Does Not Progressively Accumulate With Multiple-Doses

Acetaminophen plasma concentrations reach steady state within 10 to 15 hours of repeated dosing in neonates, infants, children, and adults. Therefore, additional doses beyond this time will not result in progressive accumulation in the body. This is consistent with the fundamental principle that the extent of accumulation (Ac) is related to a drug's half-life (t½) and the dosing interval (τ):

$$Ac = \frac{1}{1-2^{-\varepsilon}}, \quad \text{where } \varepsilon = \tau / t_{½}.$$

This relationship predicts minimal accumulation of acetaminophen for children ages 6 months to 11 years due to the short half-life and dosing interval. With a half-life of 2 to 3 hours, accumulation will range from 1.33 to 1.66 for dosing every four hours and from 1.14 to 1.33 for dosing every six hours.

Published studies have evaluated multiple-dose pharmacokinetics of oral, rectal, and intravenous acetaminophen in children < 2 years of age [8,9,18,31,32,33,34], and most investigators reported no progressive accumulation over time, except one [31]. However, the latter investigator published only his subset (N=6) of pharmacokinetic data from the McNeil-sponsored, Study P80220 for the 10-15 mg/kg dose [23], so conclusions on partial study data should be interpreted with caution.

Low accumulation of acetaminophen with repeated dosing was confirmed with a multiple-dose pharmacokinetic analysis of data in children who received the 10-15 mg/kg dose every four hours in Study P80220 [23]. Results for 18 children whose data could be modeled are summarized in Table 4-6 by age group, and they show that maximum acetaminophen exposure ($C_{MAX,ss}$) for the last dose was similar between children ages 6-23 months and 2-6 years after 2 to 3 days of repeated dosing. Importantly, the median accumulation ratio (Ac) was also similar between these pediatric age groups, and indicated low accumulation of about 19% with a range of 3% to 70% across individuals. Moreover, they are comparable to those predicted and reported for adults, because the terminal half-life of acetaminophen in adults is typically within 2 to 3 hours as well.

Table 4-6. Multiple-Dose Pharmacokinetic Modeling of Children Receiving 10-15 mg/kg Every 4 Hours; Median [Minimum, Maximum]

Age Group	N	$C_{MAX,ss}$ (µg/mL)	Half-Life (h)	Accumulation (Ac)
Children 6-23 mo	11	11.7 [8.4 to 19.1]	1.63 [0.79 to 3.12]	1.22 [1.03 to 1.70]
Children 2-6 y	7	13.9 [7.8 to 19.5]	1.08 [0.77 to 2.47]	1.08 [1.03 to 1.48]
All Children	18	12.0 [7.8 to 19.5]	1.51 [0.77 to 3.12]	1.19 [1.03 to 1.70]

4.6 Acetaminophen Concentration-Response in Children

The clinical application of linking pharmacokinetics to pharmacodynamics, or concentration-response, is to develop appropriate dosing regimens that produce desired therapeutic outcomes. For acetaminophen, data for fever reduction and pain relief in children and adults are available to explore this relationship, and they are summarized in this section. In addition, for the first time, pediatric data in children ages 6-23 months were evaluated, compared with results in children ages 2-11 years, and reported below.

4.6.1 Pharmacodynamic Models for Concentration-Response

It is well-established clinically that decreasing temperature after a dose of an antipyretic follows a pattern more closely related to the body's ability to radiate excess heat than to the faster rate of changing plasma drug concentrations. Therefore, when acetaminophen concentrations are compared at time-matched temperature differences, the fever reduction curves are shifted to later times. A similar delay has been observed between time-matched curves of acetaminophen concentrations and pain relief in surgical pain studies [35,36,37].

Both the sigmoid EMAX and EMAX models have been used to evaluate the concentration-response relationship of acetaminophen in children and adults, and these pharmacodynamic models are able to adjust for the time delays between observed concentrations and responses. The following parameters are obtained from the models:

- EC50 is the acetaminophen concentration needed to reduce fever or pain intensity by 50% of the maximum response.
- t½,keo is the half-life in minutes for the changing acetaminophen concentrations and temperature differences to synchronize.
- Gamma (γ) is a measure of the degree of concavity of the sigmoid response time in the sigmoid EMAX model.

In a review of published acetaminophen studies [38], Gibb and Anderson conclude that the concentration of 5 µg/mL needed for 50% maximum response (EC50) for fever and 10 µg/mL for pain seem reasonable based on the range of acetaminophen concentrations associated with graded analgesic and antipyretic effects. Pharmacodynamic parameters from this review, and from additional published and unpublished analyses of acetaminophen in children and adults, are summarized in Table 4-7. Overall, acetaminophen concentration-response is relatively consistent for therapeutic effects across the pediatric and adult populations, ranging from 5 to 7 µg/mL for fever, and from 10 to 17 µg/mL for pain.

Table 4-7. Acetaminophen Concentration-Response in Children and Adults

Population	Age Range	Clinical Model	Response	EC50 (µg/mL)	t½, keo (h)	γ
Children [39]	2-12 y	Fever	Temperature Reduction	4.63 (0.39)	71 (7)	3.98 (0.42)
Children [40]	2-11 y	Fever	Temperature Reduction	7.09 [a] (4.80)	45 [a,b] —	2.19 [a] (1.53)
				6.29 (3.22)	43 [b] —	2.48 (1.27)
				6.92 (5.13)	42 [b] --	2.29 (1.19)
Children [35]	6-15 y	Tonsillectomy	Pain Relief	9.98 107%	53 217%	1.0 —
Adults [36]	17-46 y	Dental Surgery	Pain Relief	16.55 (2.14)	22 —	1.0 —
				9.42 (1.58)	23 —	1.63 (0.30)
Adults [37]	Not reported	Dental Surgery	Pain Relief	15.2 —	24 —	0.44 —

a: Estimates for children who received two doses of 10-15 mg/kg as the oral liquid. This cohort was included in both the integrated pharmacokinetic and pharmacodynamic analyses (N=25; Study 93308)

b: harmonic mean; mean data are listed with either % coefficient of variation or (sd) standard deviation

4.6.2 New Pharmacodynamic Modeling of Children, 6 to 23 Months

This is the first report of acetaminophen concentration-response data in children ages 6-23 months. Pediatric fever reduction data that were amenable to modeling were pooled from four unpublished studies sponsored by McNeil that also had pharmacokinetic data [23,24,25,26]. These studies are a subset of the integrated pharmacokinetic dataset described in Section 4.4.1.

Table 4-8. Integrated Fever Reduction Dataset for Acetaminophen Oral Liquid

Age Group	Total N	Gender M/F	< 5 mg/kg	10-15 mg/kg	20-30 mg/kg	30-40 mg/kg
Children 6-23 months	33	22/11	0	14 [a]	19	0
Children 2-11 years	49	27/22	1	37	10	1

a: Includes one child who was 5.5 mo of age

4.6.2.1 Analysis Methods and Results

The sigmoid EMAX model, methods, and assumptions used to analyze fever reduction linked to pharmacokinetic data in this cohort of children are described elsewhere [26]. Because mostly children ages 6 months to 6 years comprised the pooled dataset, the estimate of mean rectal temperature for afebrile children used in the modeling was based on the reported value of 37.4 ± 0.3°C for 400 children ages 1 month to 5 years [41]. The lower limit for normal temperature, 37.1°C, where one standard deviation was subtracted from the mean, was used in the estimates of EMAX values. The remaining methods are the same as those used to model acetaminophen concentration-response in children 2-11 years in McNeil Study P93303, thus allowed the pooling of results [26].

Box plots for EC50 by age group that include median and the 25th and 75th percentiles are shown in Figure 4-5. These plots show that the response to acetaminophen by children 6 23 months and 2-11 years are comparable, although the variability was higher for children 2-11 years. Summary statistics for the pharmacodynamic parameters are listed by age group in Table 4-9.

Figure 4-5. Box Plot Showing Comparable Acetaminophen Concentrations Needed for a 50% Reduction in Fever, or EC50 (µg/mL), by Age Group

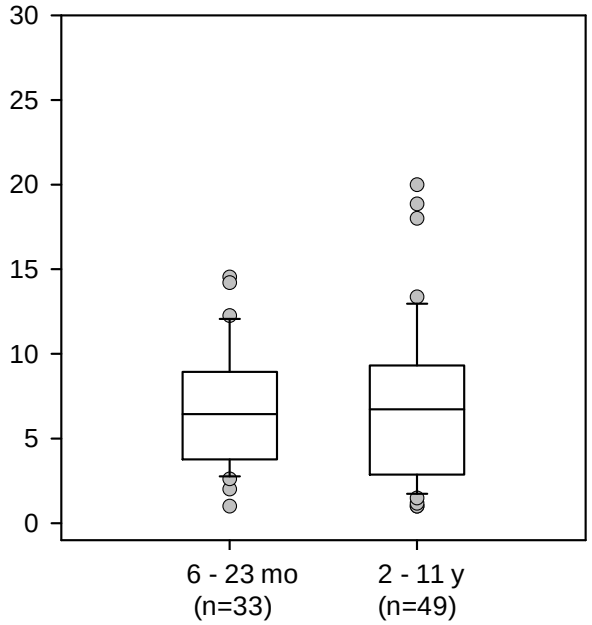


Table 4-9. Acetaminophen Pharmacodynamics by Age Group, Mean (SE) [Median]

Age Group	Total N	EC50 (µg/mL)	keo, t1/2 (min)	Gamma
Children 6-23 mo	33	6.777 (0.630) [6.439]	48 [a] — —	2.25 (0.245) [1.89]
Children 2-11 y	49	7.014 (0.664) [6.726]	53 [a] — —	2.55 (0.214) [2.48]

a: Harmonic mean

To further examine the effect of age group on EC50 for children ages 6-23 months and 2-11 years, the log-transformed EC50 was described with a linear mixed model with study as a random effect and age group as a fixed effect. Baseline temperature was included as a covariate. This model was used to calculate the geometric mean ratio and 90% confidence interval (CI) comparing log-transformed EC50 for children 6-23 months with log-transformed EC50 for children 2-11 years; the age group of 2-11 years was the reference group.

The ratio of geometric means was 107.8%, suggesting that EC50 is comparable between children ages 6-23 months and 2-11 years; however, the 90%CI were wide from 79.4% to 146.3%. Without information to define a clinically relevant boundary for concentration-response, a conclusion of equivalence cannot be drawn from this analysis.

To further examine the effect of age on EC50, a linear regression of the natural logarithm of EC50 on age was performed for children ages 5.5 months to 11 years. Results are only informative regarding EC50 for children over this age range. The slope (-1.25×10^{-3}) and its 95% CI (-6.77 to 4.26×10^{-3}) were estimated, along with the significance test of the null hypothesis that the slope is equal to zero, which was not significant at $p = 0.65$.

4.6.2.2 Conclusions Regarding Acetaminophen Concentration-Response

- An integrated analysis of acetaminophen concentration-response data across multiple McNeil-sponsored pediatric fever studies showed that the EC50 for children ages 6-23 months is similar to children 2-11 years. Importantly, these results support extrapolation of other efficacy data, like dose response, from children 2-11 years of age as the reference group.
- Published and unpublished pharmacokinetic-pharmacodynamic analyses in children and adults show that concentrations from 5-7 µg/mL are needed for 50% of maximum fever reduction, which are generally lower than concentrations from 10-17 µg/mL needed for 50% of maximum pain relief.

4.7 Evaluation of Proposed Pediatric OTC Dosing Charts by Simulating AUC With a Population Pharmacokinetic Model

This section summarizes an evaluation of McNeil's proposed pediatric OTC dosing charts through simulations with a published acetaminophen population pharmacokinetic model [18] and the McNeil pediatric pharmacokinetic dataset. The analysis was conducted by Metrum Research Group, LLC (Tariffville, CT). Simulations showed that both the weight-based and age-related charts provided appropriate doses for children, ages 6-23 months, as the median proportion of children having acetaminophen exposure that fall outside the AUC reference range were generally small.

4.7.1 Selection of the Reference Population for Simulations

The proposed weight-based and age-related acetaminophen dosing charts for children, ages 6 months to 11 years, were developed in the early 1980's [1] supported by published and unpublished pediatric data for both efficacy and pharmacokinetics. The goal was to provide consistent doses within the 10-15 mg/kg range.

Since then, there has been an evolution in the computational techniques and approaches to determine appropriate pediatric doses. Pharmacometrics is an emerging science designed to inform decisions by conducting quantitative analyses, including simulation techniques, of pharmacokinetic, pharmacodynamic, efficacy, and safety data [42]. One goal is to examine different pediatric dosing regimens that provide a distribution of drug exposures that are comparable to a distribution of exposures for a reference population with efficacy data. For new drugs with no or limited efficacy data in children, the reference is an adult population.

The cohort of children ages 2-11 years who received the 10-15 mg/kg dose of acetaminophen (N=43) was selected as the reference population for the evaluation of pediatric acetaminophen doses for children ages 6-23 months. This decision was based on the extensiveness of well-controlled clinical efficacy and safety data of acetaminophen in this cohort, and that children ages 2-11 years may be more representative of younger children. Therefore, the exposure reference range was defined as the 5^{th} and 95^{th} percentiles of observed AUC in children ages 2-11 years, which was 20.0 and 81.2 µg·h/mL, respectively.

4.7.2 Selection of the Acetaminophen Population Pharmacokinetic Model

The McNeil pediatric acetaminophen datasets (Studies P00102, P80220, P81224, P82227, P93308, and P94455) were merged and formatted for an external predictive check analysis of the two published acetaminophen population pharmacokinetic models by Anderson and

colleagues [18,19]. The purpose of this check was to assess the ability of the selected model to predict observed data through simulations.

One thousand (1000) Monte Carlo simulation replicates of this dataset were generated using each acetaminophen population pharmacokinetic model. Distributions of the median, maximum, and minimum concentrations (C_{MED}, C_{MAX}, and C_{MIN}) across all data points within each individual of the simulated data were compared with the distribution of C_{MED}, C_{MAX}, and C_{MIN} in the observed dataset using QQ plots. The QQ plots for C_{MAX} comparing the Anderson 2000 [18] and Anderson 2009 [19] models are shown in Figure 4-6 as Plot (A) and Plot (B).

Comparison of predicted results between the 1st and 3rd quartiles indicate that the Anderson 2000 model is superior in predicting acetaminophen C_{MAX}, whereas the Anderson 2009 model underestimates C_{MAX}. This trend was similar for C_{MED} and C_{MIN}; therefore, the Anderson 2000 model was selected because it is more reliable for simulations using the pediatric dosing charts. A brief description of the Anderson 2000 population pharmacokinetic model [18], and assumptions and limitations are discussed in more detail in Section 4.9.2.

4.7.3 Simulation Plan for Evaluating OTC Dosing Charts for Children, Ages 6-23 Months

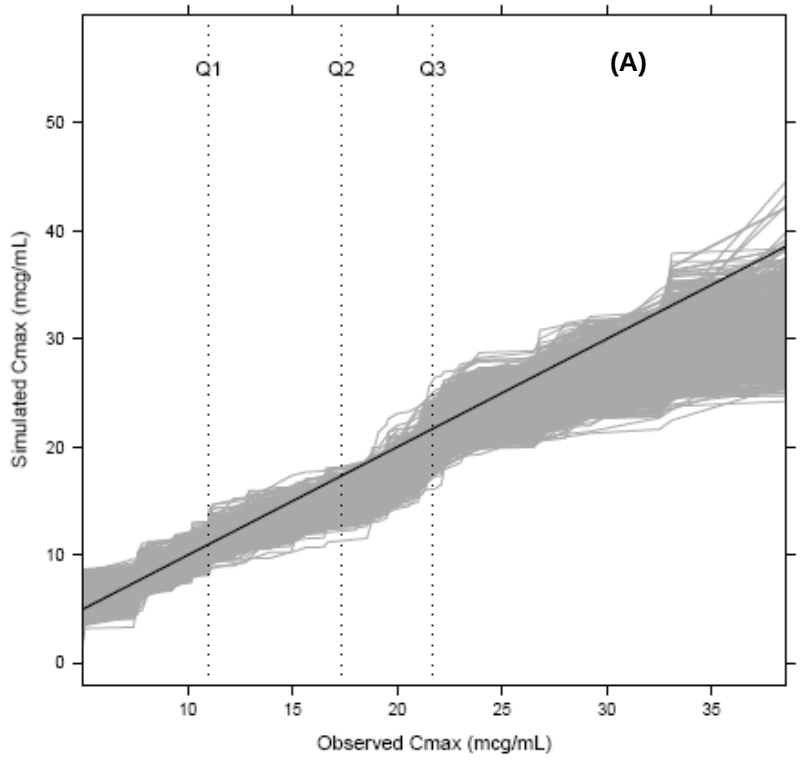
Doses provided by the proposed weight-based and age-related, 40-mg increment OTC charts for children ages 6-23 months were evaluated through simulations of acetaminophen exposure (AUC_{INF}). For the weight-based chart, the simulation plan included

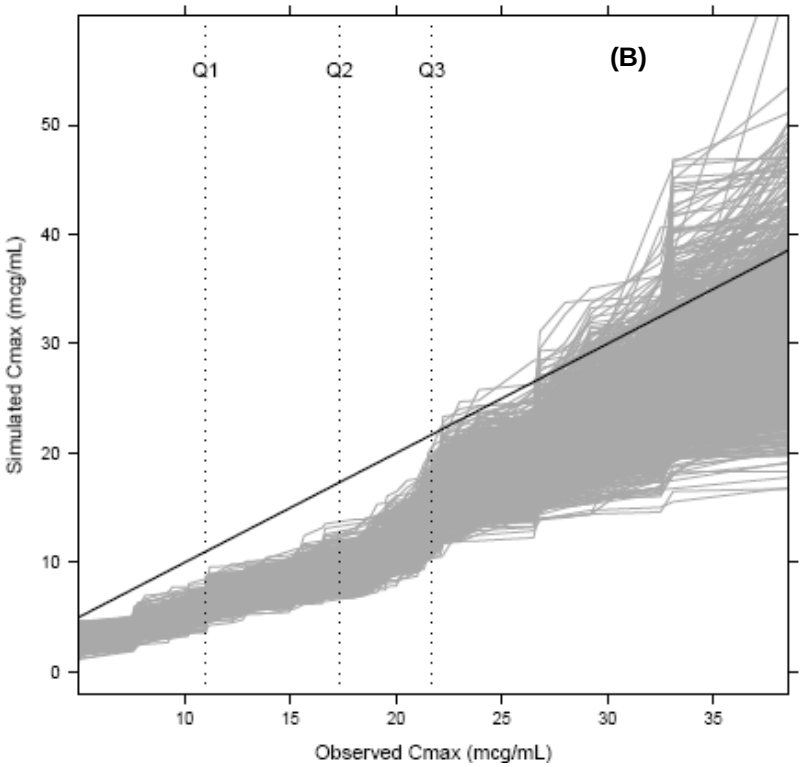
- using the WHO[2] weight-age distributions for children ages 6-23 months [43];
- dosing by weight: 12-17 lb (80 mg), 18-23 lb (120 mg), 24 lb and up[3] (dosed according to the five-division, 80-mg increment chart for children ages 2-11 y);
- using the reference exposure range of the 5th and 95th percentiles of observed AUC in children ages 2-11 years, 20.0 and 81.2 µg·h/mL, respectively;
- basing the population proportions that fall outside the reference range on 1000 simulated trials with 18000 patients per trial.

For the age-related chart, the simulations plan was the same except that dosing was by age: 6-11 months (80 mg) and 12-23 months (120 mg).

[2] World Health Organization
[3] See Section 4.9.2.2 for discussion of the choice of doses for children who are between the ages of 11-23 months who weigh more than 23 pounds

Figure 4-6. External Predictive Check for Simulated CMAX in Children Ages 6-23 Months Using Anderson's Published Models: 2000 (A) and 2009 (B). Solid Black Line Represents the Reference Line of Identity. Dotted Vertical Lines are the 1st Quartile, Median, and 3rd Quartile of the Observed CMAX Values.





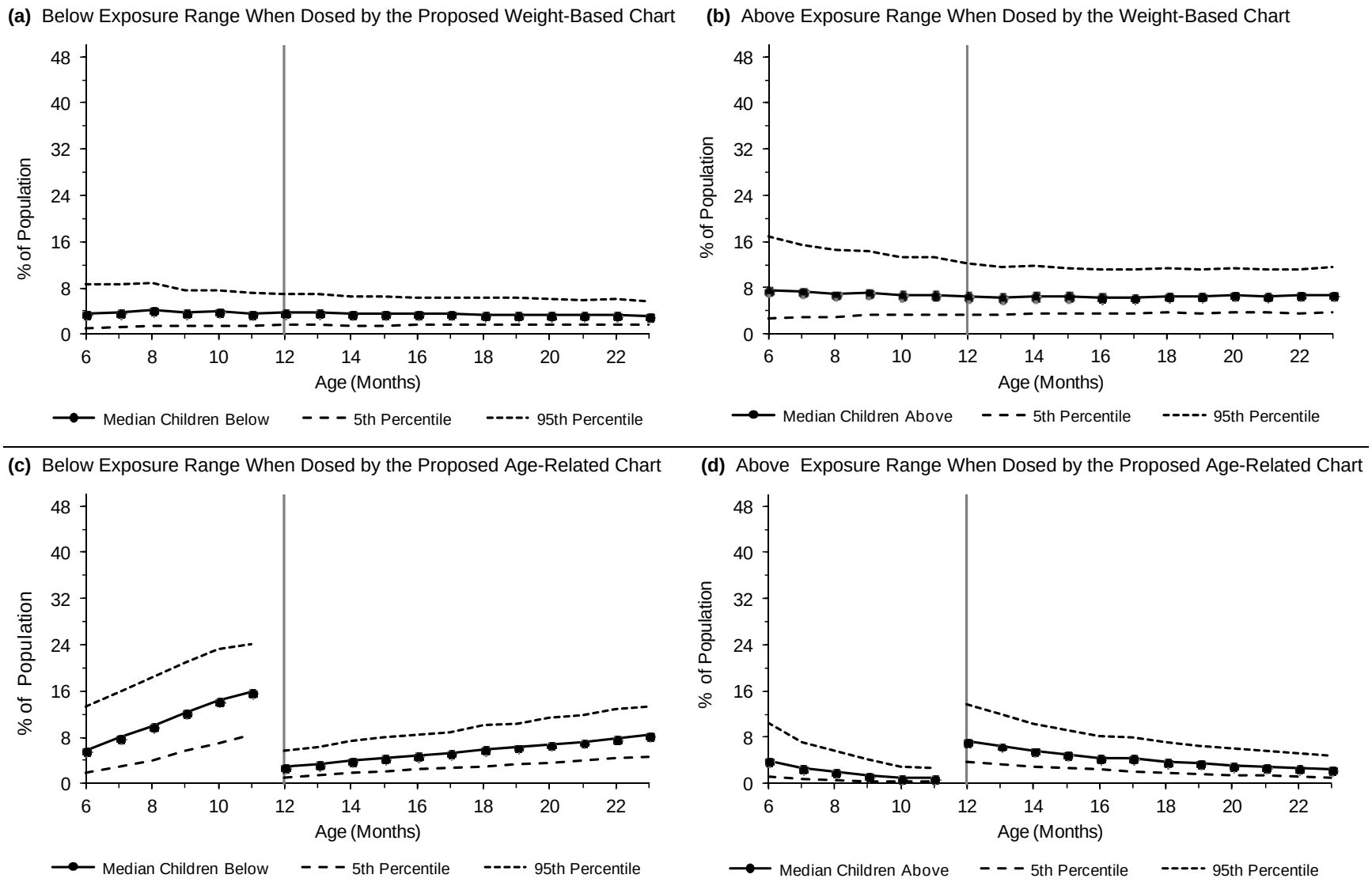
4.7.4 Simulation Results and Conclusions

Acetaminophen exposures were simulated using doses from the proposed weight-based and age-related OTC dosing charts for children ages 6-23 months, and the distribution of weights by age according to WHO [43]. From these simulations, the proportions of children below the 5th percentile and above the 95th percentile of the reference acetaminophen exposure in children ages 2-11 years were calculated. The median, and the 5^{th} and 95^{th} percentiles, of the percent of children across all 1000 simulated trials with 18000 subjects per trial that fall outside the reference exposure range were determined at each month of age.

Simulation results are displayed in Figure 4-7 as two graphs for the weight-based dosing chart for children ages 6-23 months, showing the median of the percent of children at each month of age that falls below and above the reference range (AUC for children ages 2-11 years). Similarly, two graphs for the age-related chart for children ages 6-23 months are displayed illustrating the same type of results.

These simulations demonstrate that both the proposed weight-based and age-related OTC dosing charts provide appropriate doses for children ages 6-23 months. The median proportion of children having acetaminophen exposure that fall outside the reference AUC range of children ages 2-11 years are generally small.

Figure 4-7. Median of %Children, Ages 6-23 Months, Below and Above the Reference AUC Exposure Range for Children, Ages 2-11 Years



4.8 Conclusions

An integrated analysis of acetaminophen exposure across multiple McNeil-sponsored pediatric and adult studies demonstrated that the 10-15 mg/kg dose provided children ages 6-23 months with comparable exposure as that in children ages 2-11 years. Furthermore, an integrated analysis of acetaminophen concentration-response data across a subset of these studies found that children ages 6-23 months responded similarly to acetaminophen as did children 2-11 years. Importantly, results from each analysis support extrapolation of antipyretic efficacy from children 2-11 years of age as the reference group at the 10-15 mg/kg dose. This is the first report of acetaminophen concentration-response data in children ages 6-23 months.

An acetaminophen population pharmacokinetic model that describes acetaminophen exposure and accounts for age and body size effects on clearance was use to evaluated the proposed weight-based and age-related OTC dosing charts for children 6-23 months. The cohort of children ages 2-11 years provided reference exposure range. Simulations using the model and McNeil pediatric database demonstrated that both charts provide appropriate doses for children ages 6-23 months that target 10-15 mg/kg.

4.9 Additional Information from the Analyses

4.9.1 Summary of Pediatric Pharmacokinetic-Pharmacodynamic Studies

A brief summary of the pediatric studies and subjects that were included in the integrated pharmacokinetic dataset follows. Data for each study, except P93308, were reanalyzed using WinNonlin (Version 5.2, Pharsight, Inc).

4.9.1.1 Study P00102

In the late 1970's, the bioavailability and antipyretic effectiveness of acetaminophen in eligible children 1 to 10 years of age with symptoms of upper respiratory tract viral infection were evaluated [22]. The 21 enrolled children ranged in age from eight months to seven years of age. They were randomly assigned to one of the following three treatments: a single oral dose of acetaminophen elixir at 10 mg/kg dose (N=9), 20 mg/kg dose (N=6), and 30 mg/kg dose (N=6). Rectal temperatures were recorded initially and at 0.5, 1, 2, and 4 hours, and blood samples were collected at 0.5, 1, 2, and 4 hours.

Data for two subjects could not be modeled (Subjects 306269 and 316283), so estimated parameters for 19 subjects were available for the integrated, classical pharmacokinetic analysis and the pharmacodynamic analysis.

4.9.1.2 Study P80220

In the early 1980's, the bioavailability and antipyretic effectiveness of acetaminophen were evaluated in a double-blind, single- and multiple-dose study. Children were randomized to one of two dosing regimens of the acetaminophen oral elixir: Group 1 received 12-15 mg/kg every four hours and Group 2 received 24-30 mg/kg every eight hours for up to three days [23]. At designated times over two to three days, pharmacokinetic blood samples were collected, and rectal temperature, blood pressure, and pulse measured.

Of the 48 enrolled subjects, 40 completed the study and 38 had acetaminophen plasma concentrations. Estimated parameters for all 38 subjects were available for the integrated, classical pharmacokinetic analysis and the pharmacodynamic analysis.

4.9.1.3 Study P81224

In the early 1980's, a randomized double-blind study was designed to compare three doses of acetaminophen in 27 children [24]. Temperature was measured rectally and blood samples were collected for up to 12 hours after the dose. The study was ended prior to completing the planned enrollment. Seventeen subjects completed, of which 14

had both plasma and temperature data available for analysis. They had been randomly assigned to one of the following three treatments: a single oral dose of acetaminophen elixir at 10 mg/kg dose (N=4), 20 mg/kg dose (N=7), and 30 mg/kg dose (N=6).

Estimated parameters for 12 subjects were available for the integrated, classical pharmacokinetic analysis, whereas those for Subjects 224P1014 and 224P1016 were excluded because they received doses (4.1 and 38.1 mg/kg, respectively) that were significantly outside of the two nominal dose levels in the integrated analysis. However, these subjects were eligible for the pharmacodynamic analysis.

4.9.1.4 Study P82227

In the early 1980's, a randomized double-blind study was designed to compare three doses of acetaminophen in 60 children [25]. Subjects were stratified into two age groups (6 months to 3 years and 3-5 years) and randomized to one of three acetaminophen doses 15 mg/kg, 30 mg/kg, and 40 mg/kg. Temperature was measured rectally and blood samples were collected for up to eight hours after the dose.

The study was ended prior to completing the planned enrollment. Twenty subjects completed, of which eight had both plasma and temperature data available for analysis. The plasma concentration-time data after a single dose of acetaminophen elixir at 10 mg/kg dose (N=3) and 30 mg/kg dose (N=3) were analyzed using a one-compartment model. Estimated parameters for eight subjects were available for the integrated, classical pharmacokinetic analysis and the pharmacodynamic analysis.

4.9.1.5 Study P93308

In the early 1990's, a randomized open-label study was designed to compare three formulations of acetaminophen [26]. Twenty-five febrile children were randomized to two 10-15 mg/kg doses of the oral elixir.

4.9.1.6 Study P94455

From a personal communication [27], acetaminophen plasma concentration-time data and subject demographic information were available for 12 healthy children between the ages of three months and two years. They received a single-dose of 10-15 mg/kg acetaminophen as an oral liquid prior to immunization. The data were analyzed using a one-compartment model and lag time with WinNonlin. Estimated parameters for eight subjects were available for the integrated, classical pharmacokinetic analysis. Subject 455P0006 was excluded because the modeling failed due to limited number of samples. Estimated parameters for Subjects 455P0012, 455P0015, and 455P0027 were excluded because these children were from three to four months of age, which placed them significantly outside of the nominal age range of 6-23 months.

4.9.2 Population Pharmacokinetic Model and Simulations of Pediatric Doses

4.9.2.1 Evaluation of the Population Pharmacokinetic Model

A summary of the acetaminophen population pharmacokinetic model (Anderson 2000) [18] and assumptions made for the simulations are highlighted below:

The structural pharmacokinetic model was a standard one-compartment model with first order input, absorption lag time, and first order elimination. From this model, the between-subject variability (BSV) was quantified for clearance (CL), distribution volume (V), absorption half-life (Tabs), and absorption lag-time (Tlag). Between-occasion variability was also quantified for CL and V, but this was left out of the present simulation model because most of the pediatric studies were single dose.

Both weight and age (postnatal in months) were included in the structural pharmacokinetic model as predictors of CL and V. Age was also found to influence Tabs, but was not relevant to the present simulation model because the effect was for infants $\leq$ 3 months of age, and data for infants of these ages were not present in the McNeil pediatric acetaminophen datasets.

Residual variability was modeled using an additive error model, and was modeled separately for each McNeil pediatric study included in the pooled analysis. For the simulation model, the average of the reported residual variability was used (1.5 µg/mL), which is near the LLOQ of acetaminophen reported in two of the pediatric studies (P81224 and P82227).

BSV was modeled using a proportional error model. For the simulations, an exponential error model was used to prevent simulation of negative parameter values. The exponential error model approximates a proportional model and is also more commonly used in population pharmacokinetic analyses for modeling BSV.

4.9.2.2 Other Considerations for the Simulations

The upper weight limit on the proposed weight-based dosing chart is 23 pounds. So when using the WHO age-weight distributions [43] to simulate weights for children, ages 6-23 months, a significant number of weights > 23 pounds were simulated. This discrepancy is due to the upper limit on the chart being the 10th percentile[4] weight of a 24-month-old child instead of the 90th percentile weight of a 23-month-old child. Two dosing options were considered to address this discrepancy in modeling, because it would be inappropriate to truncate the simulated weights to fewer than 23 pounds when evaluating the weight-based dosing chart. Therefore, children ages 11 to 23 months

[4] The choice of the 10th percentile weight of a 24-month-old child being the upper limit of the weight-based chart for children 6-23 months is to avoid an overlap in weights with the weight-based chart for children 2-11 years.

with simulated weights > 23 pounds could be dosed either with a maximum dose of 120 mg acetaminophen or with a dose according to the weight-based dosing chart for children, ages 2-11 years. The first option would result in slightly greater percent of underdosing, so the second option was selected for the simulations of acetaminophen exposure.

4.10 Reference List

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SECTION 5
SAFETY OF ACETAMINOPHEN IN CLINICAL TRIALS THAT INCLUDED CHILDREN LESS THAN 2 YEARS OF AGE

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5 SAFETY OF ACETAMINOPHEN IN CLINICAL TRIALS THAT INCLUDED CHILDREN LESS THAN 2 YEARS OF AGE

A considerable body of published and unpublished clinical trial data and over 50 years of clinical use support the use of acetaminophen at single and multiple doses of 10-15 mg/kg in children ages 6 months to 11 years of age.

5.1 Safety of Recommended Doses of Acetaminophen Proven in Clinical Trials

The safety of acetaminophen in children has been demonstrated in many clinical trials. Table 5-1 provides a summary of the available safety information from clinical trials that included children less than 2 years of age. The Boston Fever Study included 28,130 children treated with acetaminophen, of which 9,127 were less than 2 years of age. In the unpublished and published studies, the number of children less than 2 years of age was not always stated as these studies may have included both children less than 2 years of age and children 2 years or older in the study population.

Table 5-1. Summary of Available Safety Information in Clinical Trials That Included Children Less Than 2 Years of Age

Source	Number of Trials	Number of Children Treated with Acetaminophen
McNeil Unpublished Trials	13	622
Published Trials	71	14,010
Boston Fever Study[a]	1	28,130

a: The Boston Fever Study is also a published trial but is presented separately because of the large number of children enrolled and the specific number of acetaminophen-treated children less than 2 years of age is known.

Thirteen unpublished McNeil clinical trials were identified which evaluated the use of acetaminophen in fever reduction. Eleven were single-dose trials [1[1], 2, 3, 4, 5, 6, 7, 8, 9, 10, 11] and 2 were multiple dose trials [12, 13]. Altogether the trials enrolled 1439 children ranging from 6 months to 12 years of age. Of the 622 children who received acetaminophen, 439 received a dose in the range of 10-15 mg/kg, 147 received a dose in the range of 20-30 mg/kg, and 36 received age-based dosing of 80 mg for children less than 2 years of age and 160 mg for children 2 to less than 4 years of age. Each of the 13 unpublished McNeil clinical trials was reviewed for mentions of adverse events during the trials. No serious adverse events were reported in children treated with acetaminophen. The most common adverse events reported were gastrointestinal

[1] References are cited individually to provide the reader with a link to the reference citation in the electronic version of the document.

(nausea, vomiting, and diarrhea). When measured in the trial, renal function and liver function were not adversely affected.

Seventy-one published trials were identified which evaluated the use of acetaminophen in children for treatment of fever. Trials that stated evaluations of only children 2 years or older were not included. Of the 71 trials, 48 were single-dose trials [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61], 7 had both a single-dose and multiple-dose component [62, 63, 64, 65, 66, 67, 68], and 16 were multiple-dose trials [69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84]. The children ranged in age from 1 week to 16 years. The majority (50 of 71, 70%) of the trials evaluated acetaminophen doses in the range of 10-15 mg/kg while 11 used age-based dosing. A total of 13,909 children received oral acetaminophen alone as a treatment. Each of the 71 published clinical trials was reviewed for mentions of adverse events during the trials. Eleven trials did not report safety [20, 23, 29, 31, 35, 43, 45, 46, 48, 53, 60]. The most commonly reported adverse events were gastrointestinal (nausea, vomiting, diarrhea, abdominal pain). Serious adverse events were reported by 4 children [25, 71, 73]. One trial [28] reported 3 deaths due to systemic Epstein-Barr viral infection; bacterial endocarditis and myocardial abscesses; and complicated respiratory infection, sepsis, and respiratory failure. Hematological, biochemical, or other laboratory values were assessed in 14 trials and were not adversely affected [24, 50, 52, 54, 55, 59, 62, 68, 69, 74, 76, 81, 82, 84]. In 9 trials that evaluated liver function [50, 52, 54, 59, 62, 69, 74, 81, 84], 5 of 532 acetaminophen-treated subjects experienced abnormal liver biochemical tests. Two subjects treated with acetaminophen 10 mg/kg and 1 subject treated with 15-20 mg/kg were reported to have experienced mild and transient elevations (values not reported). Two subjects whose dose was not stated had increases in transaminases due to viral hepatitis.

One of the largest pediatric trials ever conducted, The Boston University Fever Study [85], demonstrated the safety of the acetaminophen 10-15 mg/kg dose. This was a practitioner-based randomized clinical trial that evaluated serious adverse events resulting in hospitalization for children administered acetaminophen 12 mg/kg or ibuprofen at 2 separate doses (5 mg/kg and 10 mg/kg). The children in the study were seen as outpatients by a physician for an acute febrile illness. Patients were enrolled by 1735 pediatricians, family physicians, and general practitioners from throughout the United States. This study enrolled 84,192 children less than 12 years of age of which 28,130 received acetaminophen. An analysis of the 27,065 children less than 2 years of age at the time of enrollment has been reported [86] and is presented in Table 5-2. Of the 27,065 children less than 2 years of age, 9127 were randomized to acetaminophen

12 mg/kg, 9159 to ibuprofen 5 mg/kg, and 8779 to ibuprofen 10 mg/kg. Dosing instructions allowed repeat doses at an interval of 4 to 6 hours to a maximum of 5 doses per day. In the 4 weeks after enrollment, 385 subjects were admitted to a hospital for any reason. The absolute risk of hospitalization for any reason was 1.4% (95% CI, 1.1-1.6%) with acetaminophen and 1.5% (95% CI, 1.3-1.6%) with ibuprofen. Of the 319 subjects less than 6 months of age, 2 subjects treated with ibuprofen were hospitalized, 1 with a viral infection and the other with pneumonia. No subjects were hospitalized for acute renal failure, anaphylaxis, or Reye's syndrome. Three subjects treated with ibuprofen were hospitalized with evidence of gastrointestinal bleeding. None of the subjects less than 6 months of age were hospitalized for any of the primary study outcomes. The absolute risk of hospitalization for asthma/bronchiolitis with acetaminophen was 260 per 100,000 (95% CI, 170-390) and 230 per 100,000 (95% CI, 160-310) with ibuprofen. The absolute risk of hospitalization for vomiting/gastritis with acetaminophen was 22 per 100,000 (95% CI, 2.6-79) and 39 per 100,000 (95% CI, 16-80) with ibuprofen. No subjects less than 6 months of age were hospitalized with asthma, bronchiolitis, or vomiting/gastritis.

Table 5-2. Summary of the Boston Fever Study Analysis of Children Less Than Two Years of Age

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Median Age (Range) Gender	Study Results
Lesko et al Pediatrics 1999;104: e39.	Randomized, Double-Blind, Active-Controlled, Parallel, Multicenter	APAP 12 mg/kg q4-6h	suspension oral	(9127)	14 m 4198F, 4929M	**Study Population:** Subjects 6 months to <2 years old with a febrile illness. **Safety:** A median of 6-10 doses were received over a median of 3 days. In the 4 wks after enrollment, 385 subjects were admitted to a hospital for any reason. Absolute risk (95% CI) of hospitalization for any reason: APAP-1.4% (1.1-1.6%), IBU-1.5% (1.3-1.6%). Of the 319 subjects <6 months of age, 2 IBU-treated subjects were hospitalized (viral infection and pneumonia). No subjects were hospitalized for acute renal failure, anaphylaxis, or Reye's syndrome. 3 IBU-treated subjects were hospitalized with evidence of gastrointestinal bleeding. None of the subjects <6 months of age were hospitalized for any of the primary study outcomes. Absolute risk/100,000 of hospitalization for asthma/bronchiolitis: APAP-260 (95% CI 170-390), IBU-230 (95% CI 160-310). Absolute risk/100,000 of hospitalization for vomiting/gastritis: APAP-22 (95% CI 2.6-79), IBU-39 (95% CI 16-80). No subjects <6 months of age were hospitalized with asthma, bronchiolitis, or vomiting/gastritis. Mean creatinine level at admission (µmol/L): APAP-30, IBU-37; p=NS. **Comments:** Subjects were followed for 4 weeks. 319 children were reported to be <6 months of age when enrolled in the study, had a reported weight between the 5th and 95th sex-specific percentile for month of reported age, and were included in the analysis to maximize identification of all potentially serious adverse clinical events.
		IBU 5 mg/kg q4-6h	suspension oral	(9159)	13 m 4213F, 4946M	
		IBU 10 mg/kg q4-6h	suspension oral	(8779)	13 m 3951F, 4828M	
		Multiple Dose		**Overall:** (27,065)	**Overall:** 13 m (1 m-23 m) 12362F, 14703M	

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SECTION 6
NEED AND SUPPORT FOR WEIGHT-BASED ACETAMINOPHEN DOSING IN CHILDREN LESS THAN 12 YEARS OF AGE

TABLE OF CONTENTS

6 NEED AND SUPPORT FOR WEIGHT-BASED ACETAMINOPHEN DOSING IN CHILDREN LESS THAN 12 YEARS OF AGE

6.1 Previous FDA Statement

- A "Checklist for Choosing Over-the-Counter (OTC) Medicine for Children," is available on FDA's website [1]; it advises parents and caregivers to use a child's weight to find the right dose of medicine on the Drug Facts label. If the child's weight is not known or the label does not show a dose by weight, they are instructed to use age to find the right dose.

6.2 Key Points

- Inclusion of weight-based dosing in addition to age-related dosing on OTC pediatric Drug Facts labels is important for all age groups, ie, for children 6 months to 11 years of age.

- When compared with age-related dosing, the weight-based dosing schedule provides more consistent dosing in the targeted 10-15 mg/kg dosing range for most children.

- McNeil recommends that children be dosed according to weight first, then by age if weight is not known. Weight-based dosing helps minimize doses below and above the target dosing range of 10-15 mg/kg.

- McNeil and other OTC companies have provided weight-based and age-related dosing directions on OTC single-ingredient acetaminophen medicines for children 2 to 11 years of age since 1984.

- Pediatricians and professional associations support adding a weight-based dosing schedule to the OTC pediatric acetaminophen label. They recommend using the weight-based dosing schedule when weight is known and limiting age-related dosing to use when weight is not known.

- Emergency room studies indicate that 73% to 85% of parents can estimate the weight of their child within 10% of their measured weight.

- Caregiver research confirms that when dosing is provided on the *infants'* medicines OTC label for children 6 to 23 months of age, caregivers are able to select the correct dose, and indicates that caregivers prefer weight-based dosing.

- Caregiver research indicates that caregivers' ability to select the correct dose, ease of understanding of the label, and usefulness of the label in providing the information needed to dose their child were maintained with labels with both weight-based (primary) and age-related (secondary) dosing in separate charts on acetaminophen *infants' and children's* medicines labels compared with age-only dosing directions. In addition, caregivers report that weight-based dosing is important for *infants' and children's* medicines and many use weight to dose when doses by weight and age are discordant.

6.3 Scientific Rationale for Using a Weight-Based Schedule in Preference to an Age-Related Scheduled

As detailed in Section 7, when compared with age-related dosing, a weight-based acetaminophen dosing schedule provides more consistent dosing between 10-15 mg/kg for most children. A comparison of the proposed weight-based and age-related dosing for OTC single-ingredient acetaminophen for use in children 6 months to 11 years of age is provided in Table 7-4. Thus, while age-related dosing is effective, a weight-based dosing schedule, when possible, is preferred since it helps minimize doses below and above the target dosing range of 10-15 mg/kg.

6.4 Pediatricians and Professional Associations Recommend Weight-Based Dosing

As summarized in Table 6-1, professional associations recommend weight-based dosing for acetaminophen in children.

Table 6-1. Professional Associations that Recommend Weight-Based Dosing of Acetaminophen in Infants and Children

Association	Statements
American Academy of Pediatrics (AAP)	• Supports the use of antipyretics to improve the comfort of the febrile child. States that acetaminophen doses of 10 to 15 mg/kg per dose given every 4 to 6 hours orally are generally regarded as safe and effective. [2] • Caregivers who understand that dosing should be based on weight rather than age or height of fever are much less likely to give an incorrect dose. [2] • AAP's healthychildren website for caregivers currently contains a section on medications used to treat fever which states: "Acetaminophen can be given without a doctor's advice once your child is older than three months, and ibuprofen can be given to children older than six months of age." In addition, an acetaminophen dosing chart is provided by age and weight for children 0-5 months, 6-11 months, and 1-2 years. It is noted that dosing for fever should be based on current weight and that age is provided as a convenience only. [3]
International Evidence-Based Group for Neonatal Pain [4]	• Recommends the use of acetaminophen for postoperative pain associated with circumcision. States that the recommended analgesic dose for neonates is 10 to 15 mg/kg orally or 20 to 30 mg/kg rectally.

Gribetz and Cronley [5] from the Children's Hospital of Philadelphia conducted a study of 96 children ages 5 years and younger seen in the hospital emergency department for fever. When asked about their management of fever, 92% of caregivers reported administering acetaminophen. Of these, 67% gave less than the recommended dose of 10-15 mg/kg. Underdosing was particularly common for lower weight children. The authors recommended that prescribers calculate the acetaminophen dose for a small child on the basis of weight, and indicated their preference for a 15 mg/kg dose instead of a 10 mg/kg dose. In addition, they recommended that bottles of acetaminophen be labeled with dose information for infants based on weight.

In March 2011, McNeil conducted an internet survey of 152 pediatricians who spent at least 25% of their time in direct patient care and who recommended OTC pain/fever relievers containing acetaminophen for children 12 years of age or younger in an average week [6]. The average age of the pediatricians was 46.2 years and 58% were men. Seventy-three percent of the pediatricians were in private practice, the mean number of years of practicing medicine was 16.4, and the mean percent of time in direct patient care was 95%. The mean number of recommendations for OTC pain relievers

containing acetaminophen made by the pediatricians for children 12 or younger in an average week was 65. These pediatricians were asked separately for children's (age 2 to 11 years old) and infants' (6 to 23 months) OTC single-ingredient products, how medication directions should instruct caregivers to determine the correct dose for their child. As shown in Table 6-2, 98% and 97% of pediatricians preferred that weight-based dosing be included on the OTC single-ingredient acetaminophen label, either alone or in combination with age for infants' and children's medicines, respectively. Only 2% and 3% of pediatricians preferred that medication directions instruct caregivers to determine the correct dose for their child based on age alone. For infants' medicines, 70% of pediatricians preferred weight alone, whereas for children's medicines, the percentages were similar for pediatricians that preferred weight alone (52%) and those that preferred weight and age (45%).

Table 6-2. Results of Internet Survey of 152 Pediatricians Concerning How Dosing for infants' and Children's OTC Single-Ingredient Acetaminophen Medications Directions Should Instruct Caregivers to Determine the Correct Dose for Their Child [6]

Dosing Based Upon the Child's:	Infants' (6 to 23 months) %	Children (2 to <12 years) %
Weight if known by the caregiver, and age if weight not known	28	45
Weight only	70	52
Age only	2	3

6.5 Recent Pharmaceutical Reference Textbooks Recommend Weight-Based Dosing

Table 6-3 provides a summary of recent recommendations for weight-based and age-related pediatric acetaminophen dosing reported in pharmaceutical reference textbooks. Weight-based dosing was reported in all 7 of these recent reference textbooks. Dosing by age was reported in 4 of these textbooks. In Drug Facts and Comparisons 2011, it is stated that dosing by weight is preferred over age [13]. As shown is Table 6-3, all but one of these reference textbooks provided dosing for children less than 2 years of age. Data from these reference textbooks support that weight-based dosing is appropriate and should be included on the OTC labeling.

Table 6-3. Summary of Recommendations for Weight-Based and Age-Related Pediatric Acetaminophen Dosing as Reported in Pharmaceutical Reference Textbooks

Year	Reference Source	Weight	Age	Dosing Provided for Children < 2 Years of Age
2007	Nelson Textbook of Pediatrics [7]	Yes	--[a]	Yes
2009	Current Diagnosis & Treatment Pediatrics [8]	Yes	--	--
2009	Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care [9]	Yes	--	Yes
2009	The Harriet Lane Handbook: A Manual for Pediatric House Officers [10]	Yes	Yes	Yes
2009	Martindale: The Complete Drug Reference [11]	Yes	Yes	Yes
2011	AHFS Drug Information 2011 [12]	Yes	Yes	Yes
2011	Drug Facts and Comparisons 2011 [13]	Yes	Yes	Yes

a: -- = not mentioned in textbook.

6.6 Weight-Based Dosing is Currently Available for OTC Pediatric Analgesics on Packaging and on the Internet

Weight-based and age-related dosing schedules are currently provided on OTC acetaminophen medicines for ages 2 to 11 years. Weight-based dosing was added to these medicines in 1984. In addition, OTC ibuprofen medicines for children less than 2 years of age and for medicines for children ages 2 to 11 years also have weight-based and age-related dosing on the Drug Facts label. The Infants' Motrin Concentrated Drops medicine was approved in 1999 with both weight-based and age-related dosing schedules. The weight and age breaks proposed for acetaminophen for both the infants' and children's medicines are the same as those approved by FDA and in use for pediatric Motrin medicines.

As noted previously in Section 2.4.1, the internet is an additional source of acetaminophen dosing information used by caregivers, and the internet frequently provides weight-based dosing for children 6 months to 11 years of age.

6.7 A Majority of Caregivers Can Estimate Their Child's Weight within 10% of Their Measured Weight

A potential concern related to weight-based dosing is that caregivers do not always know the weight of their child. Data from 6 published studies indicate that most parents can provide a reasonable estimate their child's weight. These 6 emergency department studies are summarized in Table 6-4. Five of these 6 studies reported on the ability of parents to appropriately estimate their child's weight within 10% of measured weight, with percentages of 85.2%, 80%, 79%, 78%, and 73.4% [14,15,16,17,18]. The 6th study reported that 84% of parents estimated their child's weight within 15% of actual weight [19]. Two studies evaluated the effect of the child's age on these weight estimates and both reported no statistically significant effect [16,19].

Table 6-4. Summary of Studies of Parental Estimates of their Child's Weight

Study	Location	Years of Study	No. of children	Age, years	Results
Trakulsrichai [14]	Bangkok, Thailand	2009[a]	595	Not stated	85.2% of parents estimated their child's weight within 10% of the measured weight.
Leffler [15]	Burlington, Vermont	1996	117	0-5	80% of parents estimated their child's weight within 10% of the measured weight.
Partridge [16]	Nashville, Tennessee	2007	812	0-20	79% of parents and 83% of guardians estimated their child's weight within 10% of the measured weight.
Krieser [17]	Melbourne, Australia	2005/2006	364	1-10	78% of parents estimated their child's weight within 10% of the measured weight.
Goldman [18]	Ramat-Gan, Israel	1999[a]	233	Not stated	73.4% of parents estimated their child's weight within 10% of their measured weight; 51.5% within 5% of their measured weight, and 87.5% within 20% of their measured weight.
Harris [19]	Bethlehem, Pennsylvania	1996	100	0-8	84% of parents, 60% of nurses, and 71% of physicians were within 15% of the child's actual weight.

a: year of publication; the year the study was conducted was not reported.

Each of the 6 studies listed in Table 6-4 are summarized in the following paragraphs. In 2009,Trakulsrichai et al reported the results of a study at an emergency room and a general outpatient pediatric clinic in Bangkok, Thailand involving family members of 595 children ages neonates to 12 years [14]. Overall, 85.21% of family members estimated the weight of their child within 10% of their measured weight. A mean difference of -0.26 kg compared with measured weight was reported.

Leffler and Hayes conducted a study in 1996 in an emergency department of a tertiary care hospital in Burlington, Vermont involving parents of 117 children from ages 5 days to 60 months [15]. The mean age of children was 26.7 months. Eighty percent of parents estimated the weight of their child within 10% of the measured weight.

Krieser et al conducted a study in 2005 to 2006 in an emergency department of a metropolitan community teaching hospital in Melbourne, Australia involving parents of 364 children ages 1 to 10 years of age [17]. The mean age of children was 4.5 years. Seventy-eight percent of parents estimated the weight of their child within 10% of the measured weight. A mean difference of -0.6 kg compared with measured weight was reported.

In 1999, Goldman et al reported on the results of a study (year of study not provided) conducted in a pediatric emergency department in Ramat-Gan, Israel involving parents of 233 children (age not stated) [18]. In this study, 51.5% of parents estimated their child's weight within 5% of the measured weight, 73.4% within 10%, and 87.5% within 20%. A significant difference was noted between maternal and paternal estimates, with 56.1% of mothers and 40.3% of fathers estimating their child's weight within 5% of their actual weight ($p<0.05$). Weight was overestimated by mothers 34.1% of the time and underestimated 9.8% of the time. Fathers overestimated weight 30.6% of the time, and underestimated weight 29% of the time.

Partridge et al conducted a study in 2007 at an urban children's hospital in Nashville, Tennessee involving parents/guardians of 812 children ages 4 days to 20 years [16]. The mean age of the children was 5.64 years. Seventy-nine percent of parents and 83% of guardians estimated the weight of their child within 10% of their measured weight. The authors noted that the child's age did not affect the weight estimates ($p = 0.95$).

Harris et al conducted a study in 1996 in an urban hospital emergency department in Bethlehem, Pennsylvania involving caregivers of 100 children ages 0 to 8 years [19]. Mean percentage deviations from actual weights were significantly ($p < 0.05$) lower than actual weights for all groups of caregivers (nurses: -7%, parents: -1.3%, and doctors: -

4.8%), but there was no statistically significant difference among groups. However, estimates of the child's weight for 84% of parents, 60% of nurses, and 71% of physicians were within 15% of the child's actual weight. Participants were divided into 5 equal age groups with respect to age in months, and no statistically significant difference in weight accuracy estimations was found among the age groups.

6.8 Published Research Indicates that 87% of Caregivers Correctly Interpret Weight-Based and Age-Related Dosing on the Label

Madlon-Kay and Mosch conducted a study in 1996 in waiting areas of 3 clinics in St. Paul, Minnesota [20]. The 3 clinics were chosen to provide a variety of socioeconomic and ethnic backgrounds and included 1 private clinic serving a predominately white middle-class suburban population, a residency clinic serving primarily a white lower-socioeconomic population, and a community clinic serving mostly Hmong and Hispanic patients. There were 130 participants in the study. The mean age of participants was 40 years and 105 were women. Participants had a mean of 1.1 children in the household. The study evaluated the ability of caregivers to correctly interpret a pediatric dosing chart for a liquid. Participants were shown a dosing chart that had dosing listed by both age and weight and contained a note that dosing by weight was more accurate. Participants were asked to indicate the correct dose for 2 children for whom weight and age were provided. In 1 example the child's age and weight matched on the chart, and in the second example the age and weight were discordant (eg, a higher dose based on the child's weight than based on the child's age). The pediatric dosing chart was correctly interpreted by 87% of the participants for both examples. For the example where age and weight were discordant, 12% of participants gave the dose based on age rather than weight.

6.9 Recent McNeil Consumer Research on Weight-Based and Age-Related Dosing Charts for Pediatric Single-Ingredient Acetaminophen Liquid Medicines

McNeil conducted research on caregivers and pediatric dosing charts in 6 locations[1] throughout the United States during the period March 23-26, 2011 [21]. Acetaminophen labels (labeled generically as Infants' Pain Relief) with infants' dosing charts with dosing increments of 40 mg and 20 mg were evaluated since 40 mg increments were consistent with the dosing schedule that has been in use since 1983 and 20 mg increments were recognized as a potential alternative to 40 mg increments in the March 2007 FDA Nonprescription Drug Clinical Review: Acetaminophen-Induced Hepatotoxicity [22]. This

[1] Locations included: Bala Cynwyd, Pennsylvania; Atlanta, Georgia; San Francisco, California; Houston, Texas; Salt Lake City, Utah; and Deerfield, Illinois.

March 2007 clinical review stated that, "FDA is currently drafting a proposed rule that will include 20 mg dosing increments for APAP dosing for children 6 to 23 months of age."

The overall study objective was to understand if enhancements to the pediatric OTC acetaminophen single-ingredient label would help caregivers in selecting a correct dose for their child.

Specific areas of interest were as follows:

Infants only

- Caregivers' preference concerning "ask a doctor" versus dosing provided on the label
- How caregivers select a dose when dose is not provided on the label

Infants and children

- Caregivers' ability to select the correct dose for their child
- Caregivers' assessment of whether the label provides the information they need to give their child a correct dose
- Caregivers' assessment of the ease of understanding the label
- Caregivers' assessment of the importance of having weight and age on the label
- How caregivers select a dose when the dose by weight of their child does not agree with the dose by age of their child

6.9.1 Consumer Research Study – Key Findings and Implications

1) Most caregivers (91%) select the correct dose with an infants' weight and age dosing chart with two 40 mg dosing increments.

   When given two infants' dosing charts, one with dosing instructions for ages 6 to 23 months and a second that says "ask a doctor", and asked which provides the information they need to select a correct dose for their child:
   - 91% of caregivers chose the dosing chart with 6 to 23 month instructions
   - 5% of caregivers chose the dosing chart that says "ask a doctor"

   Only 12% to 27% of caregivers agree that an infants' analgesic dosing chart with "ask a doctor" for dosing instructions for a child under the age of 2 provides them the information they need to select a correct dose for their child.

2) A substantial portion of caregivers use their own means, versus contacting their doctor, for dosing instructions.

Over one-third of caregivers report they have given their child a medication that did not have dosing instructions on the label. These caregivers reported doing the following to obtain dosing instructions:

- 63% reported asking their doctor
- 23% reported figuring the dose out on their own, using the internet/other reference, or calling a friend/relative

Approximately one-quarter of low literacy caregivers recalled giving their child a medication that did not contain dosing instructions. These caregivers reported doing the following to obtain dosing instructions:

- 52% reported asking their doctor
- 31% reported figuring the dose out on their own, using the internet/other reference, or calling a friend/relative

3) Caregivers want both age and weight information to provide the information needed to select a correct dose for their child. When asked which is the most important for selecting a correct dose for their child, caregivers responded as follows:
   - 80% of caregivers believe weight is most important for selecting a dose
   - 4% of caregivers believe both weight and age are equally important
   - 15% of caregivers believe age is most important for selecting a dose

4) Having both weight-based (primary) and age-related (secondary) dosing in separate charts on an infants' label does not complicate a caregiver's ability to select a correct dose for their child versus an age-only dosing chart.

   There were no statistically significant differences between the age-only dosing charts versus the comparable dosing chart with both weight-based (primary) and age-related (secondary) dosing in separate charts (see Table 6-6).

5) However, having both weight-based (primary) and age-related (secondary) dosing in separate charts with 20 mg dosing increments resulted in a statistically significantly lower rate of caregivers selecting a correct dose for their child versus 40 mg dosing increments.

   When shown a infants' label with both weight-based (primary) and age-related (secondary) dosing in separate charts, the percentage of caregivers able to select a correct dose when shown two 40 mg dosing increments was significantly greater (p-value = 0.017) than for caregivers shown four 20 mg dosing increments:
   - 91% correct dose selected for infants' label with two 40 mg dosing increments
   - 81% correct dose selected for infants' label with four 20 mg dosing increments

   This may be due, in part, to the fact that discordance between the weight and age dosing instruction was significantly greater (p-value < 0.001) for the 20 mg increment (64%) versus the 40 mg increment (39%).

The implications of the study are as follows:

- Adding weight-based instructions to an infants' age-only analgesic label with 6 to 23 month dosing instructions does not complicate the caregiver's ability to select the correct dose.
- Most caregivers want both weight and age instructions on the infants' analgesic label to provide them the information they feel is most appropriate for dosing their child.
- When dosing information is not present on the label, a substantial portion of caregivers will use their own means, versus contacting their doctor, to make a dosing decision.
- Dosing intervals for an infants' analgesic weight and age chart should be provided in 40 mg increments to maximize a caregiver's ability to select a correct dose for their child.

6.9.2 Consumer Research Study Methods

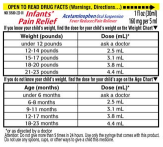
This multi-center study included 1055 caregivers with children 6 months to less than 12 years of age. Two sets of pediatric labels were evaluated in this study. Arm 1 of the study evaluated pediatric labels that provided age-only dosing. Arm 2 of the study evaluated pediatric labels that had both weight-based (primary) and age-related (secondary) dosing in separate dosing charts. Within each arm of the study, there were 4 cells. The 8 cells of the study, a description of the label evaluated, the age of the respondent's child, and the number of participants per cell are provided in Table 6-5.

Participants were identified through review of databases available at each study site and were screened for eligibility using a standard script. If eligible, participants were invited to participate in the study and asked to schedule an appointment to participate in the study at the study site and to bring their child with them on that day. A moderator-guided interview was conducted using a standard questionnaire. Participants in each arm and cell of the study received a bottle with complete labeling as would be provided on a bottle purchased for an OTC pediatric single-ingredient acetaminophen medicine. If requested, participants were provided the labeled carton that would have contained the bottle when purchased. Participants were provided with a scale to weigh their child only if requested. The dosing charts (booklet label), ie, a portion of the Drug Facts label for each cell of the study, are provided in the approximate size provided to participants in Section 6.11.1.

Participants were asked questions concerning the labeling materials according to the arm and cell of the study to which they were assigned. The interviewer did not

determine if the participant provided the correct dose. The interviewer collected and recorded the age of the child reported by the participant at screening. The dose selected by the caregiver for their child was collected during the interview. The interviewer recorded the participant-reported weight of the child after the participant provided the selected dose for their child. The categorization of whether or not the dose selected by the caregiver was correct was a computer-based assessment derived from the reported age and/or weight of the child and the cell (and label) to which they were assigned. The interviewer also recorded if the participant stated that their proposed dose was the dose their doctor told them to give; in such instances, the dose was categorized as correct, regardless of the dose specified.

Table 6-5. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts - Summary of Study Cells Including Dosing Chart Assessed, Age of Respondent, and Number of Participants

Cell	Label Assessed	Age of Respondent's Child	Number of Participants	Thumbnail Image Dosing Charts[a]
Arm 1:	**Age-only Pediatric Dosing Chart**			
1	Infants' label with "ask a doctor" dosing instructions for a child <24 months of age	6-23 mos	103	
2	Children's label with currently used age breaks	2-11 yrs	167	
3	Infants' label with age breaks and 20 mg dosing increments for children 6-23 months	6-23 mos	121	
4	Infants' label with age breaks and 40 mg dosing increments for children 6-23 months	6-23 mos	141	
Arm 2:	**Both Weight-based (Primary) and Age-related Dosing (Secondary) in Separate Charts**			
5	Infants' label with "ask a doctor" dosing instructions for a child <24 months of age	6-23 months	104	
6	Children's label with currently used weight and age breaks	2-11 yrs	158	
7	Infants' label with weight and age breaks and 20 mg dosing increments for children 6-23 months	6-23 mos	121	
8	Infants' label with weight and age breaks and 40 mg dosing increments for children 6-23 months	6-23 mos	140	

a: Dosing charts of the approximate size of the charts used in the study are provided in Section 6.11.1.

6.9.3 Consumer Research Study Results

6.9.3.1 Demographic and Baseline Characteristics

Eighty-seven percent of the 1055 participants were women, 63% were Caucasian, 22% were African American, and 15% were of other races. Twelve percent of participants were of Hispanic ethnicity. The median age of participants was 34 years, with a range of 19 to 74 years. Five percent of participants had not graduated from high school, 14% had graduated from high school, and 81% had at least attended some college/technical school. Forty-seven percent of participants had only 1 child; 35% had 2 children. Ninety-seven percent of participants indicated that they had a regular doctor for their child. Fifty-four percent of participants reported an annual household income of $65,000 or less, 6% reported $15,000 or less, and 6% reported between $15,000 and $25,000. Eleven percent (n=118) of participants were considered to be of low literacy based on the REALM test[2]. Participants with low literacy were more likely to be African American (45%), Hispanic (20%), less educated (41% high school graduate or less than high school graduate), and with lower annual household income (32% $25,000 or less) when compared with those of a higher level of literacy.

6.9.3.2 Consumer Understanding of Labels

6.9.3.2.1 Selecting the Correct Dose

Table 6-6 provides a summary of the percentage of participants who selected the correct dose upon reading the label for all participants and the low-literacy subgroup. Participants in cells 2-4 and 6-8 were shown the label specified for their cell, and asked to read the label and indicate the dose they would give their child. Eighty-one percent or more of all participants in each of these cells correctly selected the appropriate dose to give their child.

Most caregivers (91%) selected the correct dose with an infants' weight and age dosing chart with two 40 mg increments. Increasing the number of dosing increments within Arm 2 (both weight-based (primary) and age-related dosing (secondary) in separate charts) (cell 7 vs cell 8) resulted in a statistically significantly ($p = 0.017$) lower percentage of correct dose selection: 81% vs 91%. This was not observed in Arm 1 (age-only chart) where the percentages (cell 3 vs cell 4) were 88% vs 87%, respectively.

[2] Rapid Assessment of Adult Literacy in Medicine (REALM) is an assessment of health literacy. Scores 0-18: ≤ 3rd grade; 19-44: 4th -6th grade; 45-60: 7th – 8th grade; 61-66: ≥9th grade. Low literacy = REALM score of ≤60.

There were no other statistically significant differences in the percentages of participants with a correct dose selection.

The percentage of participants who selected the correct dose upon reading the label was lower in all cells for the participants with low literacy by 5% to 30% compared with the percentages for all participants. Statistical comparisons between cells were not made, since a relatively small number of subjects participated in each of these cells (8 to 25).

Table 6-6. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Percent of Participants Selecting the Correct Dose by Study Cell

		All Participants		Low Literacy	
Cell	Label Assessed	N	Correct Dose Selected % (95% CI)	N	Correct Dose Selected %
Arm 1: Age-only Dosing Chart					
2	Children's label	167	83 (76,88)	25	80
3	Infants' label – four 20 mg increments	121	88 (80,93)	8	77
4	Infants' label two 40 mg increments	141	87 (80, 92)	14	57
Arm 2: Both Weight-based (Primary) and Age-related Dosing (Secondary) in Separate Charts					
6	Children's label	158	84 (76, 90)	22	68
7	Infants' label – four 20 mg increments	121	81* (73, 88)	8	75
8	Infants' label – two 40 mg increments	140	91* (86, 96)	13	77

*Statistically significant difference between 81% (cell 7) and 91% (cell 8), p=0.017.

Question 12: Please look at this label and tell me what dose would you give your child?

6.9.3.2.2 Participant Preference Concerning Ask a Doctor Versus Dosing on Infants' Medicines

Participants in cell 1 (Arm 1; infants' label – "ask a doctor" for dosing instructions for child <24 months of age, with age-only dosing for children 2-3 years) and cell 5 (Arm 2; Infants' label – "ask a doctor" for dosing instructions for child <24 months of age, with both weight-based and age-related dosing in separate charts for children 2-3 years) were asked to compare an "ask a doctor" infants' dosing chart to the alternative infants' dosing charts in the same Arm of the study to which they were assigned. These alternative infants' dosing charts had 20 mg and 40 mg dosing intervals and had an age-only dosing chart (Arm 1; labels 3 and 4) or both weight-based and age-related dosing in separate charts (Arm 2; labels 7 and 8). Table 6-7 provides a summary of the responses of participants when asked: "Please look at each of these labels and tell me which label provides you the information you need to give your child a correct dose?" Table 6-7 shows that 89% and 93% of participants preferred labels with actual doses in comparison to labels with "ask a doctor" information for dosing for children less than 2 years of age. Findings were similar for participants with low literacy with 86% in Arm 1 and 93% in Arm 2 preferring either of the 2 labels with dosing information for infants (data not shown).

Table 6-7. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Response to Question on Which Infants' Label Provides the Information Needed to Give a Correct Dose by Study Arm and Cell

Response	Arm 1 Label 1 vs Label 3 or 4 %	Arm 2 Label 5 vs Label 7 or 8 %
Either of the 2 labels with dosing information for infants	93	89
Current label with "ask a doctor" as the dosing direction	5	6
Both labels are the same	2	5

Question 11: Please look at each of these labels and tell me which label provides you the information you need to give your child a correct dose?

6.9.3.2.3 Does the Label Provide Information Needed to Select the Correct Dose

Participants were asked to rate how much they thought the label they had reviewed provided the information that they needed to dose their child. As summarized in Table 6-8, the percentages of all participants who strongly agreed or somewhat agreed that the label provided the information needed to dose their child were higher for all alternative infants' dosing charts (cells 3, 4, 7, and 8) and ranged from 75% to 91% compared with the age-only infant dosing charts (cells 1 and 5) with "ask your doctor" directions for children 6 to 23 months of age (12% and 27%), respectively. The percentage of participants who strongly agreed or somewhat agreed that the label provided the information needed to dose their child was slightly higher for the children's label with both weight-based and age-related dosing in separate charts (86%) (cell 6) compared with the age-only children's dosing chart (83%) (cell 2). Results were similar for participants with low literacy.

Table 6-8. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Percent of Participants Who Strongly Agreed or Somewhat Agreed That the Label Provided the Information Needed to Dose Their Child by Study Cell

		All Participants		Low Literacy	
Cell	Label Assessed	N	Strongly/ Somewhat Agreed %	N	Strongly/ Somewhat Agreed %
Arm 1:	**Age-only Dosing Chart**				
1	Infants' label – "ask a doctor"	103	12	7	0
2	Children's label	167	83	25	92
3	Infants' label – four 20 mg increments	121	75	8	84
4	Infants' label two 40 mg increments	141	87	14	86
Arm 2:	**Both Weight-based (Primary) and Age-related Dosing (Secondary) in Separate Charts**				
5	Infants' label – "ask a doctor"	104	27	16	25
6	Children's label	158	86	22	91
7	Infants' label – four 20 mg increments	121	91	8	100
8	Infants' label – two 40 mg increments	140	90	13	92

Question 13: This label gives me the information I need to give my child a correct dose.

6.9.3.2.4 Dosing by Caregivers When Dose is Not Provided on the Label

All participants (n=1055) in Arm 1 and Arm 2 were asked: "Have you ever had to give your child a medication that did not have dosing instructions on the packaging for their age or weight?" Thirty-five percent (n=369) indicated they had done so. These participants were then asked: "What did you do the first time when the infants' label did not provide dosing information for children under 2 years of age?" As shown in Table 6-9, 63% of all participants reported asking their doctor and 23% reported figuring the dose out on their own, using the internet or some other reference, or calling a friend or relative. In comparison, 52% of participants with low-literacy reported asking their doctor and 31% reported figuring the dose out on their own, using the internet or some other reference, or calling a friend or relative.

Table 6-9. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Number and Percent of Participants Responding to Question Concerning What They Did the First Time When the Infants' Label Did Not Provide Dosing Information for Children Under 2 Years of Age

	All Participants (N=369)		Low Literacy (N=29)	
Response[a]	n	%	n	%
Called the doctor's office or talked to the doctor while in the office	231	63	15	52
Figured it out on my own	46	13	6	21
Looked up on the internet or some other reference	27	7	1	3
I already had a dosing chart from the doctor	22	6	1	3
Called a friend or relative	11	3	2	7
Other	83	23	6	21

a: Participants can provide multiple responses.
Question 18a: "What did you do the first time when the infants' label did not provide dosing information for children under 2 years of age?"

6.9.3.2.5 Ease of Understanding the Label

Participants were asked to rate how easy it was to understand the label they had reviewed. As shown in Table 6-10, the percentages of all participants who strongly agreed or somewhat agreed that the label was easy to understand were higher for all alternative infants' dosing charts (cells 3, 4, 7, and 8) and ranged from 90% to 97% compared with the age-only infant dosing charts (cells 1 and 5) with "ask your doctor" directions for children 6 to 23 months of age (66% and 76%), respectively. The percentage of participants who strongly agreed or somewhat agreed that the label was easy to understand was the same (96%) for the children's label with both weight-based and age-related dosing in separate charts (cell 6) and the age-only children's dosing chart (cell 2). Results were similar for participants with low literacy.

Table 6-10. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Percent of Participants Who Strongly Agreed or Somewhat Agreed That the Label Was Easy to Understand by Study Cell

		All Participants		Low Literacy	
			Strongly/ Somewhat Agreed		Strongly/ Somewhat Agreed
Cell	Label Assessed	N	%	N	%
Arm 1: Age-only Dosing Chart					
1	Infants' label – "ask a doctor"	103	66	7	43
2	Children's label	167	96	25	100
3	Infants' label – four 20 mg increments	121	95	8	92
4	Infants' label two 40 mg increments	141	97	14	92
Arm 2: Both Weight-based (Primary) and Age-related Dosing (Secondary) in Separate Charts					
5	Infants' label – "ask a doctor"	104	76	16	81
6	Children's label	158	96	22	100
7	Infants' label – four 20 mg increments	121	94	8	100
8	Infants' label – two 40 mg increments	140	90	13	92

Question 14: This label is easy to understand.

6.9.3.2.6 Importance to Caregivers of Having Weight and Age on the Label

Participants in Arm 2 (both weight-based (primary) and age-related (secondary) dosing in separate charts - Cells 5-8) were asked questions concerning having age and weight information on dosing charts. These participants were asked: "Which do you feel is more important to decide how much medicine to give, your child's age or weight?" As shown in Table 6-11, 80% of participants reported that weight was more important and an additional 4% reported that both weight and age were important. For participants with low literacy, 62% reported that weight was more important and an additional 10% reported both weight and age were important.

Table 6-11. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Response to Question on Importance of Weight and Age in Decision on How Much Medicine to Give – Arm 2 Both Weight-Based (Primary) and Age-Related (Secondary) Dosing in Separate Charts

Which do you feel is more important to decide how much medicine to give, your child's age or weight?	All Participants %	Low Literacy %
Weight	80	62
Age	15	26
Both	4	10
Other/Do not know	1	2

Question 16: Which do you feel is more important to decide how much medicine to give, your child's age or weight?

6.9.3.2.7 How Caregivers Dose When Dose by Weight Does not Agree with Dose by Age

Forty-seven percent (n=199) of all participants in cells 6, 7, and 8 of Arm 2 reported that the dose for their child's age was not the same as the dose for their child's weight. Sixty-four percent (n=77) of all participants in cell 7 (20 mg dosing increments) and 39% (n=55) in cell 8 (40 mg dosing increments) of Arm 2 reported that the dose for their child's age was not the same as the dose for their child's weight; the difference between these two percentages was statistically significant (p-value<0.001).

Upon reporting a difference in dose by weight and age, participants in cells 6, 7, and 8 were asked: Which did you use? As shown in Table 6-12, 48% to 55% of participants used weight and an additional 3% to 4% used both age and weight. Results were similar for participants with low literacy. In this subgroup, 40% to 57% used weight and no caregivers used both age and weight.

Table 6-12. McNeil Consumer Research on Pediatric Acetaminophen Dosing Charts – Percent of Participants Who Used Weight or Both Age and Weight When Dose Differed by Weight and Age by Study Cell in Arm 2

		- - - All Participants - - -			- - - Low Literacy - - -		
Cell	Label Assessed	N	Weight %	Both Weight and Age %	N	Weight %	Both Weight and Age %
Arm 2: Both Weight-based (Primary) and Age-related Dosing (Secondary) in Separate Charts							
6	Children's label	67	48	3	7	57	0
7	Infants' label – four 20 mg increments	77	55	4	5	40	0
8	Infants' label – two 40 mg increments	55	49	4	8	50	0

Question 15a: Which did you use?

6.10 Conclusions

Inclusion of weight-based dosing in addition to age-related dosing on OTC pediatric Drug Facts labels is important for all age groups, ie, for children 6 months to 11 years of age. When compared with age-related dosing, the weight-based dosing schedule provides more consistent dosing in the targeted 10-15 mg/kg dosing range for most children. In addition, recommendations from pediatricians and professional associations support inclusion of weight-based dosing in addition to age-related dosing on OTC pediatric Drug Facts labels. Caregivers prefer weight-based dosing and consumer testing confirms the addition of weight-based dosing does not complicate caregivers' ability to select a correct dose compared to age-related dosing only. Consumer research also shows that weight-based dosing is important to caregivers for infants and children and that many use weight to dose when doses by age and weight are discordant.

6.11 Supportive Tables, Figures, and Materials

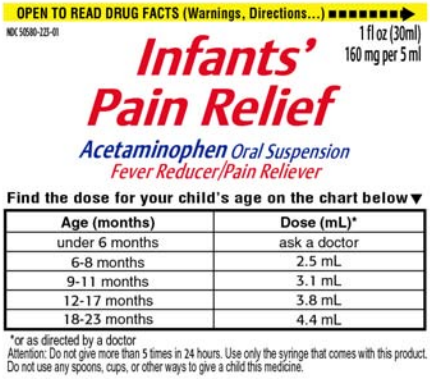
6.11.1 Consumer Research Study - Dosing Charts

6.11.1.1 Arm 1: Age-only Pediatric Dosing Charts

6.11.1.1.1 Cell 1 – Infants' label with "Ask a Doctor" Dosing Instructions for a Child Less than 24 Months of Age

6.11.1.1.2 Cell 2 - Children's Label with Currently Used Age Breaks

6.11.1.1.3 Cell 3 – Infants' Label with Age Breaks and 20 mg Dosing Increments for Children 6 to 23 Months of Age



6.11.1.1.4 Cell 4 – Infants' Label with Age Breaks and 40 mg Dosing Increments for Children 6 to 23 Months of Age

OPEN TO READ DRUG FACTS (Warnings, Directions...)

NDC 50580-225-01

1 fl oz (30ml)
160 mg per 5 ml

Infants' Pain Relief

Acetaminophen Oral Suspension
Fever Reducer/Pain Reliever

Find the dose for your child's age on the chart below▼

Age (months)	Dose (mL)*
under 6 months	ask a doctor
6-11 months	2.5 mL
12-23 months	3.8 mL

*or as directed by a doctor
Attention: Do not give more than 5 times in 24 hours. Use only the syringe that comes with this product. Do not use any spoons, cups, or other ways to give a child this medicine.

6.11.1.2 Arm 2: Weight-only Pediatric Dosing Chart (primary), with a Secondary Age-only Pediatric Dosing Chart

6.11.1.2.1 Cell 5 - Infants' Label with "Ask a Doctor" Dosing Instructions for a Child Less than 24 Months of Age

OPEN TO READ DRUG FACTS (Warnings, Directions...)

NDC 50580-225-01

1 fl oz (30ml)
160 mg per 5 ml

Infants' Pain Relief

Acetaminophen Oral Suspension
Fever Reducer/Pain Reliever

If you know your child's weight, find the dose for your child's weight on the Weight Chart▼

Weight (pounds)	Dose (mL)*
under 24 pounds	ask a doctor
24-35 pounds	5 mL

If you do not know your child's weight, find the dose for your child's age on the Age Chart▼

Age (yr)	Dose (mL)*
under 2 years	ask a doctor
2-3 years	5 mL

*or as directed by a doctor
Attention: Do not give more than 5 times in 24 hours. Use only the syringe that comes with this product. Do not use any spoons, cups, or other ways to give a child this medicine.

6.11.1.2.2 Cell 6 - Children's Label with Currently Used Weight and Age Breaks

If you know your child's weight, find the dose for your child's weight on the Weight Chart▼

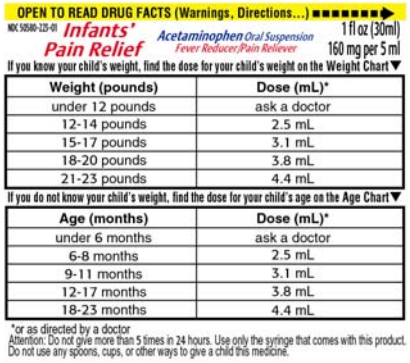
Weight (pounds)	Dose (mL or tsp)*
under 24 pounds	ask a doctor
24-35 pounds	5 mL (1 tsp)
36-47 pounds	7.5 mL (1½ tsp)
48-59 pounds	10 mL (2 tsp)
60-71 pounds	12.5 mL (2½ tsp)
72-95 pounds	15 mL (3 tsp)

If you do not know your child's weight, find the dose for your child's age on the Age Chart▼

Age (yr)	Dose (mL or tsp)*
under 2 years	ask a doctor
2-3 years	5 mL (1 tsp)
4-5 years	7.5 mL (1½ tsp)
6-8 years	10 mL (2 tsp)
9-10 years	12.5 mL (2½ tsp)
11 years	15 mL (3 tsp)

*or as directed by a doctor
Attention: Use only the cup that comes with this product. Do not use any spoons, other cups, or other ways to give a child this medicine.

6.11.1.2.3 Cell 7 – Infants' Label with Weight and Age Breaks and 20 mg Dosing Increments for Children 6 to 23 Months of Age



OPEN TO READ DRUG FACTS (Warnings, Directions...) ▶

NDC 50580-225-01

Infants' Pain Relief

Acetaminophen Oral Suspension
Fever Reducer/Pain Reliever

1 fl oz (30ml)
160 mg per 5 ml

If you know your child's weight, find the dose for your child's weight on the Weight Chart▼

Weight (pounds)	Dose (mL)*
under 12 pounds	ask a doctor
12-14 pounds	2.5 mL
15-17 pounds	3.1 mL
18-20 pounds	3.8 mL
21-23 pounds	4.4 mL

If you do not know your child's weight, find the dose for your child's age on the Age Chart▼

Age (months)	Dose (mL)*
under 6 months	ask a doctor
6-8 months	2.5 mL
9-11 months	3.1 mL
12-17 months	3.8 mL
18-23 months	4.4 mL

*or as directed by a doctor
Attention: Do not give more than 5 times in 24 hours. Use only the syringe that comes with this product. Do not use any spoons, cups, or other ways to give a child this medicine.

6.11.1.2.4 Cell 8 – Infants' Label with Weight and Age Breaks and 40 mg Dosing Increments for Children 6 to 23 Months of Age

OPEN TO READ DRUG FACTS (Warnings, Directions...) ▶

NDC 50580-225-01

Infants' Pain Relief

Acetaminophen Oral Suspension
Fever Reducer/Pain Reliever

1 fl oz (30ml)
160 mg per 5 ml

If you know your child's weight, find the dose for your child's weight on the Weight Chart▼

Weight (pounds)	Dose (mL)*
under 12 pounds	ask a doctor
12-17 pounds	2.5 mL
18-23 pounds	3.8 mL

If you do not know your child's weight, find the dose for your child's age on the Age Chart▼

Age (months)	Dose (mL)*
under 6 months	ask a doctor
6-11 months	2.5 mL
12-23 months	3.8 mL

*or as directed by a doctor
Attention: Do not give more than 5 times in 24 hours. Use only the syringe that comes with this product. Do not use any spoons, cups, or other ways to give a child this medicine.

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SECTION 7
DEVELOPMENT OF WEIGHT-BASED AND AGE-RELATED DOSING SCHEDULES

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7 DEVELOPMENT OF WEIGHT-BASED AND AGE-RELATED PEDIATRIC ACETAMINOPHEN DOSING SCHEDULES

7.1.1 Historical Recommendations

In 1983, Temple published a novel pediatric acetaminophen dosing schedule which included both weight-based and age-related dosing, and was designed to produce doses more closely correlated to the targeted dosing range of 10-15 mg/kg than previously available schedules [1]. Since 1984, McNeil has voluntarily provided these pediatric dosing schedules on labels for single-ingredient OTC Tylenol medicines for children 2-11 years of age and to healthcare professionals upon request for children less than 2 years of age.

The weight-based and age-related dosing schedules were created using distinct and separate approaches and are linked by their use of the same doses and dosing increments and by their common goal of targeting an acetaminophen dose range of 10-15 mg/kg.

The weight-based dosing schedule was created by matching incremental dosing increases of 40 mg coupled with appropriate increasing weight increments for children 6-23 months of age and increases of 80 mg coupled with appropriate increasing weight increments for children 2-11 years to maintain the dose ***within*** the 10-15 mg/kg target range. As such, the weight-based schedule for children 6-23 months uses weight increments of 6 pounds. The weight-based schedule for children 2-11 years of age uses weight increments of 12 pounds. Dosing by weight eliminates the inherent mg/kg variability of age-related dosing resulting from differing body sizes among children of the same age, especially for those children at the extremes of weight-for-age.

The age-related dosing schedule was created by matching the same incremental dosing increases of 40 mg for children 6-23 months of age and 80 mg for children 2-11 years to maintain the dose for average weight-for-age children ***within*** the 10-15 mg/kg target range and to maintain the dose for extremes of weight-for-age children ***near*** the 10-15 mg/kg target range. In 1983 when Temple developed the age-related dosing schedule, he used data from the National Center for Health Statistics (NCHS), as presented by the then most current edition of Nelson's Textbook of Pediatrics, to determine the weight-for-age of children in the 10th, 50th and 90th percentile groups. The weight used in calculating the age-related mg/kg dose for these percentile groups was the average of the weight-for-age for boys and girls.

The dosing schedule for children 2-11 years of age consists of 5 different doses (160 mg, 240 mg, 320 mg, 400 mg and 480 mg) which link the age-related and weight-based schedules. This schedule has been included on the OTC label for single-ingredient Tylenol medicines and has been used by caregivers for almost 30 years. The label contains the statement: "If possible use weight to dose; otherwise use age."

The currently proposed OTC dosing schedule for children 6-23 months consists of 2 common doses (80 mg and 120 mg) which link the age-related and weight-based schedules. A schedule similar to this has been provided to healthcare professionals and has been used for dosing children less than 2 years of age since 1984. Although healthcare providers commonly dose children by weight, instructions provided with the professional dosing schedule reinforce this principle. The proposed age and weight breaks for single-ingredient infants' acetaminophen medicines are identical to those currently in use for single ingredient infants' ibuprofen drops for children 6-23 months of age.

Table 7-1 demonstrates how the age-related schedule and the weight-based schedule are linked by their use of common doses. The approximate weight-for-age ranges of the age-related schedule are calculated by using the 10th weight-for-age percentile child of the lowest age in the range to the 90th weight-for-age percentile child of the oldest age in the range. As shown, the approximate weight ranges derived from age-related dosing are wider than those used in weight-based dosing, and overlap with the ranges above and below. Note that the weights-for-ages range for a given dose is, therefore, not the same as the weight ranges used for the weight-based schedule.

Table 7-1. Relationship of Age-Related and Weight-Based Pediatric Acetaminophen Dosing Schedules to Dose

Age-related Schedule	Approximate weights-for-ages (10^{th}-90^{th} percentile)(pounds)	Dose (mg)	Weight-based Schedule (pounds)
6-11 mo	15-24	80 mg	12-17
12-23 mo	18-30	120 mg	18-23
2-3 yrs	24-42	160 mg	24-35
4-5 yrs	31-56	240 mg	36-47
6-8 yrs	38-82	320 mg	48-59
9-10 yrs	52-107	400 mg	60-71
11	64-121	480 mg	72-95

It is important to reinforce that the weight-based schedule and the age-related schedule were created using distinct and separate approaches, and that the link between the 2 schedules in the dosing chart is the use of common doses with the goal of targeting a 10-15 mg/kg dose. Because the 2 schedules use common doses of acetaminophen, the age-related and weight-based doses have historically been displayed on the same line within the dosing chart. However, because the schedules were created with different approaches, for a given age range on the dosing chart, the weight range is close to, but does not exactly match, the weights that would be expected based upon anthropometric data (weight-for-age charts). The weight range does not, and was not designed to, match a specific age range. Because separate and independent methods were used to create the weight-based and age-related dosing schedules, the schedules could be displayed as separate tables, which may help minimize questions when the age and weight of a given child are discordant.

7.1.2 McNeil's Proposed Acetaminophen Dosing Schedules and Charts for Children 2-11 Years of Age

The currently proposed weight-based and age-related dosing chart for children 2-11 years of age is shown in Table 7-2. This chart uses weight ranges, age ranges, and doses that are identical to those which are currently used on the Children's Tylenol (160 mg/5 mL) label, and most OTC pediatric acetaminophen liquids. The only difference between the proposed chart and McNeil's current acetaminophen dosing chart is that "mL" is presented first in order, followed by "tsp" in the Dose section, to be consistent with the Consumer Healthcare Products Association (CHPA) voluntary guidelines for volumetric measures on pediatric liquid medicines. The age-related schedule within the dosing chart is the same as that proposed in the FDA's OTC IAAA Tentative Final Monograph for all OTC single ingredient pediatric acetaminophen liquids and solids intended for use in children [2].

Table 7-2. McNeil Proposed Dosing Directions and Chart: Children's Tylenol Liquid Suspension (160 mg Acetaminophen/5 mL)

- Find right dose on chart below. If possible, use weight to dose; otherwise, use age.

Weight (lb)	Age (yr)	Dose (mL or tsp)
under 24	under 2 years	ask a doctor
24-35	2-3 years	5 mL (1 tsp)
36-47	4-5 years	7.5 mL (1 ½ tsp)
48-59	6-8 years	10 mL (2 tsp)
60-71	9-10 years	12.5 mL (2 ½ tsp)
72-95	11 years	15 mL (3 tsp)

tsp = teaspoon, mL = milliliter

Figure 7-1 presents the approximate doses (mg/kg) of acetaminophen produced by using the proposed 80 mg incremental weight-based dosing schedule, relative to weight (pounds).

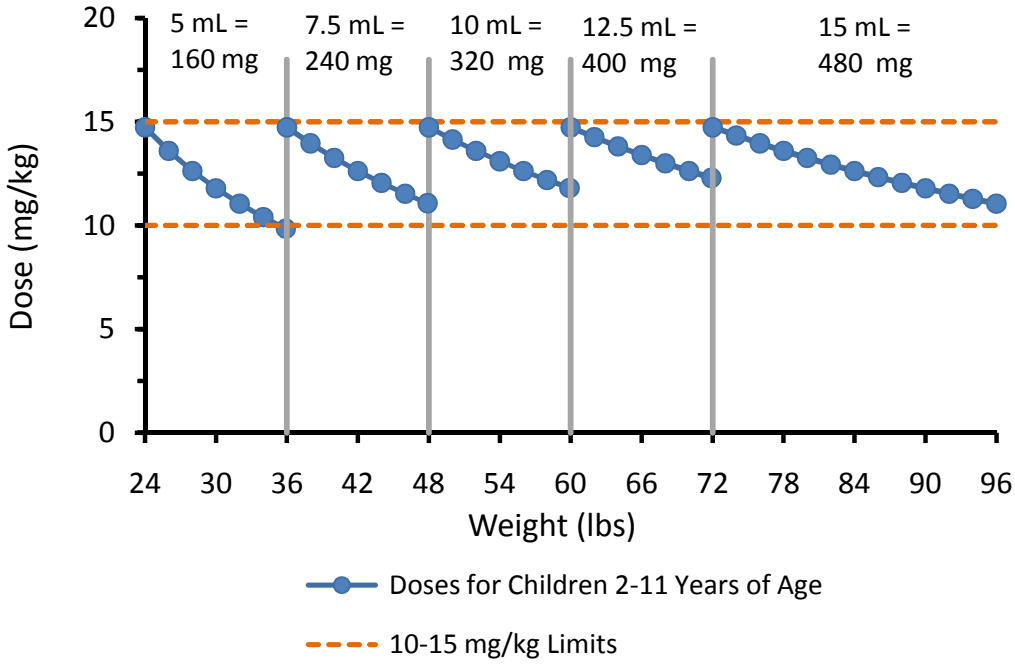

Figure 7-1. Comparison of McNeil's Proposed 80 mg Incremental Weight-Based Acetaminophen Doses for Children Weighing 24 through 96 pounds to Optimal Dosage Range of 10-15 mg/kg

Figure 7-2, using updated data from the 2000 CDC Growth Charts for children ages 2 to 20 years, provides a comparison of the proposed 80 mg incremental age-related doses of acetaminophen to optimal dosage range of 10-15 mg/kg for children 2-11 years of age at the 10th, 50th and 90th weight-for-age percentiles [3].

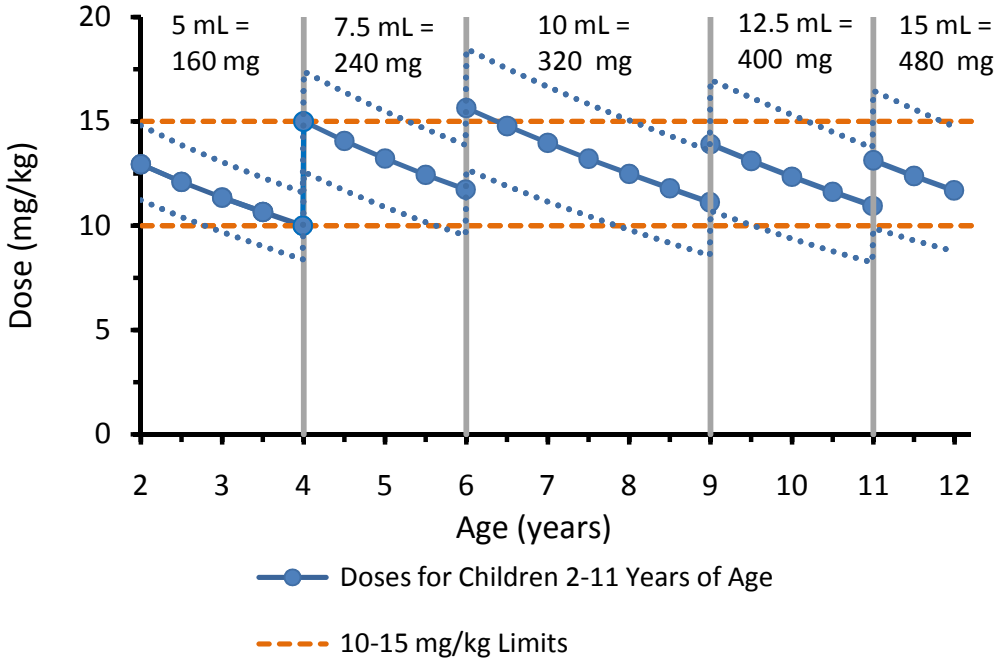

Figure 7-2. Comparison of McNeil's Proposed 80 mg Incremental Age-Related Doses of Acetaminophen to Optimal Dosage Range of 10-15 mg/kg for Children 2-11 Years of Age at 10th, 50th and 90th Percentiles

When the age-related dosing (Figure 7-2), which provides a dose *near* the target range of 10-15 mg/kg, is compared with the weight-based dosing (Figure 7-1), which remains *within* the 10-15 mg/kg range, it is clear that weight-based dosing should be considered the preferred dosing schedule when a child's weight is known.

These comparisons also indicate that the existing weight-based and age-related dosing schedules for children 2-11 years of age remain acceptable for labeling of acetaminophen products. Since the weight-based dosing chart is based on weight, it does not require adjustment based on trends in the weights of children over time. Importantly, as shown in Figure 7-2, the current age-related dosing schedule continues to produce doses *near* the 10-15 mg/kg range when calculated using data from the currently available 2000 CDC Growth Charts for Children, and therefore does not need to be changed.

7.1.3 McNeil's Proposed Acetaminophen Dosing Schedules and Charts for Children 6-23 Months of Age

Table 7-3 provides McNeil's proposed weight-based and age-related dosing schedules for children 6-23 months of age for the new single concentration (160 mg/5 mL) of single-ingredient pediatric acetaminophen liquids intended for use on OTC label of infants' products. The proposed age and weight breaks for single-ingredient infants' acetaminophen medicines are identical to those approved by the FDA in 1999 for use on the OTC label for single-ingredient infants' ibuprofen medicines [4].

Table 7-3. Proposed McNeil Dosing Chart and Directions: OTC Infants' Tylenol Oral Suspension for Children (160 mg Acetaminophen/5 mL)

- Find right dose on chart below. If possible, use weight to dose; otherwise, use age.

Weight (lb)	Age (months)	Dose (mL)
under 6 months		ask a doctor
12-17 lbs	6-11 months	2.5 mL
18-23 lbs	12-23 months	3.75 mL

Figure 7-3 presents the approximate doses (mg/kg) of acetaminophen produced by using the proposed 40 mg incremental weight-based dosing schedule, relative to weight (pounds).

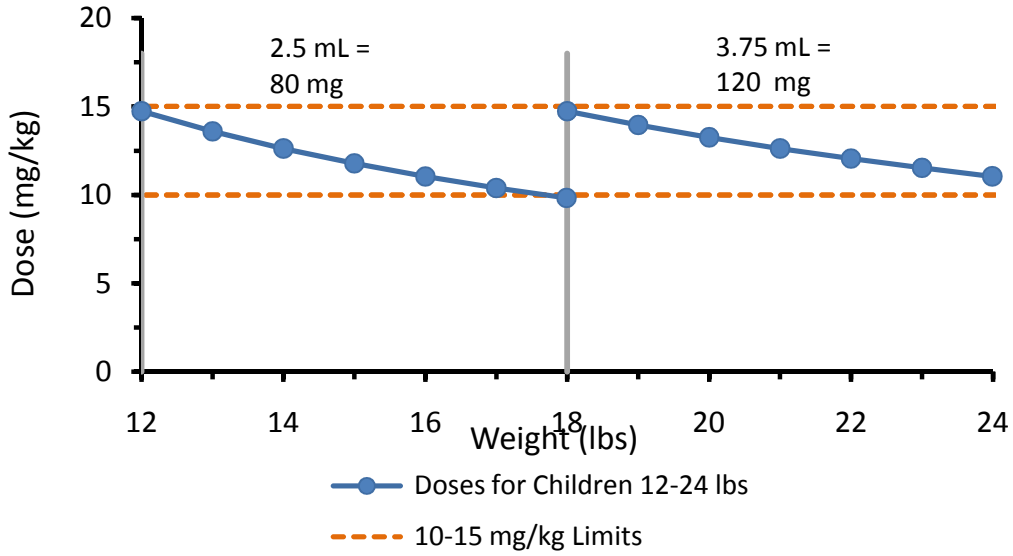

Figure 7-3. Comparison of McNeil's Proposed 40 mg Incremental Weight-Based Acetaminophen Doses in Children Weighing 12-23 pounds to Optimal Dosage Range of 10-15 mg/kg

In order to accurately reflect changes of the average weight of children in the 28 years since the publication of the 1983 dosing schedules, the mg/kg doses provided by the age-related schedules for children were calculated based on updated data from the 2006 WHO Child Growth Standards, which are currently recommended by the CDC for use in children less than 2 years of age [5]. Figure 7-4 provides a comparison of proposed 40 mg incremental age-related doses of acetaminophen to optimal dosage range of 10-15 mg/kg for children at the 10th, 50th and 90th weight-for-age percentiles (averaged boys and girls).

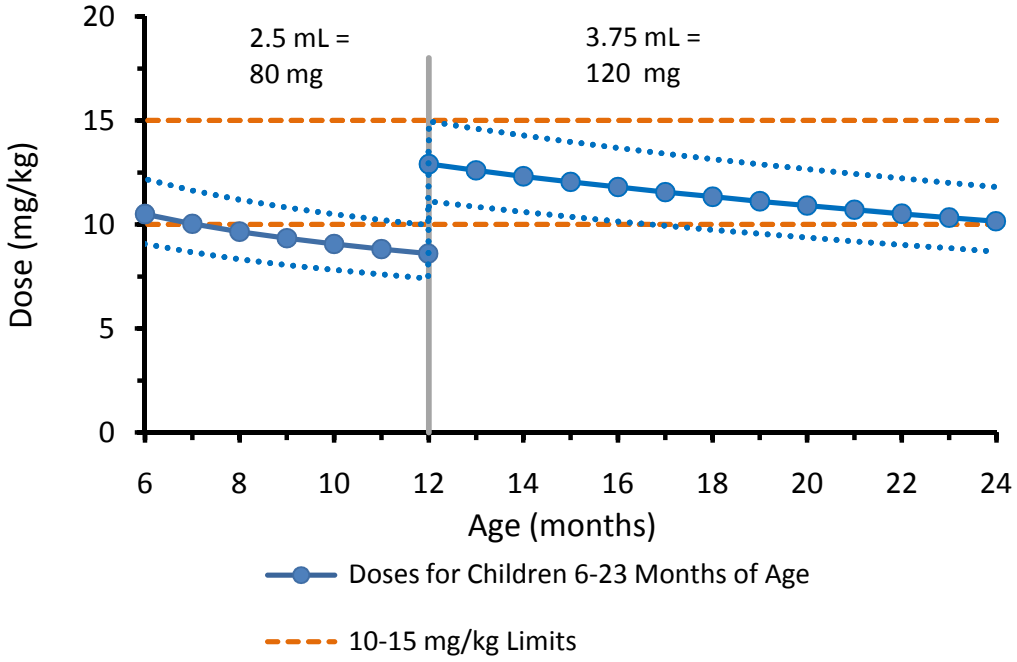

Figure 7-4. Comparison of McNeil's Proposed 40 mg Incremental Age-Related Doses of Acetaminophen to Optimal Dosage Range of 10-15 mg/kg for Children 6-23 Months of Age at 10th, 50th and 90th Percentiles

When compared with age-related dosing (Figure 7-4) which provides a dose *near* the target range of 10-15 mg/kg, weight-based dosing provides a dose which remains *within* the 10-15 mg/kg range, and should therefore be considered the preferred dosing schedule when a child's weight is known.

7.1.4 Summary of Comparison of mg/kg Dosing with Weight-Based and Age-Related Pediatric Acetaminophen Dosing Schedules for Children 6 Months to 11 Years of Age

Table 7-4 provides a comparison of the proposed weight-based and age-related dosing for OTC single ingredient acetaminophen for use in children from 6 months to 11 years of age. Weight-based dosing (Figure 7-3) maintains the dose ***within*** the 10-15 mg/kg target range and age-related dosing (Figure 7-4) maintains the dose for ***average*** weight-for-age children ***within*** the 10-15 mg/kg target range and maintains the dose for extremes (10^{th} and 90^{th} percentiles) of weight-for-age children ***near*** the 10-15 mg/kg target range.

Table 7-4. Comparison of Acetaminophen Doses (mg/kg) Provided by Weight-Based and Age-Related Dosing

Age-Related Dose Range: 10^{th}-90^{th} percentile weight for age (mg/kg)	Age	Dose	Weight (lbs)	Weight-Based Dose Range (mg/kg)
Proposed Acetaminophen Dosing for Children 6-23 months for Infants' Medicines				
7.4-12.2	6-11 mo	80 mg	12-17	10.4-14.7
8.7-15.0	12-23 mo	120 mg	18-23	11.5-14.7
Proposed Acetaminophen Dosing for Children 2-11 years for Children's Medicines				
8.4-14.8	2-3 yrs	160 mg	24-35	10.1-14.7
9.5-17.4	4-5 yrs	240 mg	36-47	11.3-14.7
8.6-18.5	6-8 yrs	320 mg	48-59	12.0-14.7
8.2-17.0	9-10 yrs	400 mg	60-71	12.5-14.7
8.8-16.5	11	480 mg	72-95	11.2-14.7

7.2 Conclusions

- The McNeil proposed weight-based and age-related dosing schedules for acetaminophen were designed with the goal of consistently producing a dose within the 10-15 mg/kg range for children across all weights and ages.
- Weight-based and age-related dosing schedules were developed using 2 distinct and separate approaches.
- Weight-based dosing should be the preferred method for selecting a dose because it avoids the variability inherent to the age-based dosing, caused by differing body sizes among children of the same age.
- Dosing schedules approximating the 10-15 mg/kg range can be created using specific dosing increments, including the proposed 40 and 80 mg schedules.
- Dosing schedules can be presented as the proposed dosing charts with a single table displaying weight-based and age-related dosing side-by-side, or in an alternative format, with weight-based and age-related dosing displayed as 2 separate tables.

7.3 Reference List

1. Temple, Anthony. Pediatric Dosing of Acetaminophen. Pediatric Pharmacology 1983;3:321-27.

2. FDA Proposed Rule OTC Internal Analgesic Monograph. July 1977.

3. Centers for Disease Control and Prevention Growth Chart Data Tables, Available at: http://www.cdc.gov/growthcharts/html_charts/wtage.htm Accessed on March 28, 2011.

4. U.S. Food and Drug Administration. Letter to McNeil Consumer Healthcare. April 15, 1999.

5. Centers for Disease Control and Prevention WHO Growth Standards. Available at: http://www.cdc.gov/growthcharts/who_charts.htm Accessed on March 28, 2011.

SECTION 8

ROOT CAUSES OF UNINTENTIONAL ACETAMINOPHEN EXPOSURES AND OVERDOSE AND MCNEIL'S RISK MITIGATION PLAN

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8 ROOT CAUSES OF UNINTENTIONAL ACETAMINOPHEN EXPOSURES AND OVERDOSE AND MCNEIL'S RISK MITIGATION PLAN

8.1 Key Points for Pediatric Root Causes of Unintentional Acetaminophen Overdose and McNeil's Risk Mitigation Plan

- Data from multiple post-marketing sources confirm that accidental unsupervised ingestions are the most common root cause of unintentional acetaminophen exposures in children.

- Data from multiple post-marketing sources confirm that medication errors, although much less common than accidental unsupervised ingestions, result in acetaminophen overdose in children.

- Liver injury in children is very rare following accidental unsupervised ingestions or medication errors.

- McNeil is committed to working with FDA and other stakeholders to proactively address and reduce unintentional acetaminophen exposures and overdose in children. McNeil's Risk Mitigation Plan is based upon and targeted to specific root causes of unintentional pediatric acetaminophen exposures and overdose and includes interventions aimed at minimizing accidental unsupervised ingestions and preventing medication errors.

- The addition of dosing directions to the OTC single-ingredient acetaminophen label for children 6 to 23 months of age will likely reduce medication errors.

8.2 Accidental Unsupervised Ingestions Identified as an Important Root Cause of Unintentional Acetaminophen Exposures and Overdose in Children

Accidental unsupervised ingestions occur when curious young children self-ingest medicines or other products that are not kept out of their reach. Children between 1 and 2 years of age are at greatest risk for accidental unsupervised ingestions with most occurring in children less than 5 years of age [1, 2].

Acetaminophen, due to its widespread availability and use in young children, is one of the most common medicines associated with accidental unsupervised ingestions in the pediatric population [2, 3, 4]. In children, accidental unsupervised ingestions involving acetaminophen, when compared to medication errors involving acetaminophen, account

for the vast majority of calls to US poison centers (72% vs 26%) [5] and emergency department visits (87% vs 3%) [2].

Although many accidental unsupervised ingestions involving acetaminophen may result in an overdose and some may require evaluation in a healthcare facility, liver injury following accidental unsupervised ingestion is very rare. An evidence-based practice guideline from the American Association of Poison Control Centers (AAPCC) recommends that children less than 6 years of age should be referred to an emergency department if the estimated amount ingested in an acute accidental unsupervised ingestion is either unknown or 200 mg/kg or more [6].

Data from multiple sources including McNeil's post-marketing database, the AAPCC and the Consumer Product Safety Commission's National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance (NEISS-CADES) confirm that accidental unsupervised ingestions are the most common root cause of unintentional acetaminophen exposures and overdoses in children [1, 2, 3, 4].

8.2.1 Company Post-Marketing Database –Root Cause Analysis of Overdose in Children – Accidental Unsupervised Ingestion 2004-2010

The company post-marketing safety database for acetaminophen was queried for the 7 year period from January 1, 2004 through December 31, 2010 for pediatric (age less than 12 years) cases from the United States. Additional methodology surrounding these post-marketing data can be found in Section 8.6.

In this dataset, accidental unsupervised ingestion accounted for 18% of all the reported adverse events for children less than 12 years of age. Eight cases (less than 1% of all the reported adverse events) reporting accidental unsupervised ingestion contained a preferred term in the Standard MedDRA Query (SMQ) for Possible Drug Related Hepatic Disorders. This illustrates that although accidental unsupervised ingestion is an important root cause for exposures and overdose in children, few develop liver injury. For the time period 2004-2010, over 1.6 billion dosage units of pediatric single-ingredient Tylenol were purchased [7]. Based upon this estimated exposure, liver injury in children is very rare following accidental unsupervised ingestions.

8.2.2 New Insights into Root Causes of Accidental Unsupervised Ingestions

To better understand the root causes of accidental unsupervised ingestion, McNeil conducted a retrospective case review of US reports in children less than 12 years of

age with OTC medicines whose parent/caregiver had contacted McNeil's call center and reported an accidental ingestion with the use of one of the company's OTC medicines.

McNeil's survey showed that most of these reported accidental unsupervised ingestions with OTC medicines occurred at home, in the bedroom or kitchen. The children had frequently been left unobserved while the caregiver was in a different room. Pediatric formulations intended for use by the child who had an accidental unsupervised ingestion were commonly involved. Although most caregivers stored their medicines in a high area out of sight, accidental unsupervised ingestions often occurred within 24 hours of the last therapeutic use when the OTC medicine was not in its normal storage location. Medicines were commonly stored within multiple rooms and not in a locked location. Caregivers stored OTC and adult medicines differently than prescription and pediatric medicines [8]. New insights into root causes of accidental unsupervised ingestions may help guide targeted interventions and educational efforts.

8.3 Medication Errors Identified as an Important Root Cause of Unintentional Acetaminophen Exposures and Overdose in Children

Medication errors in children may occur when there is an intentional or unintentional deviation from the labeled directions and a caregiver administers a medication with therapeutic intent.

Although pediatric medication errors involving acetaminophen commonly result in an overdose, and some require evaluation in a healthcare facility; liver injury following medication errors is very rare. It would be unusual for a one time medication error involving administration of greater than the single dose of 10-15 mg/kg to result in liver injury. The management of this type of medication error involving a single acute ingestion in children less than 6 years old would be similar to how an acute accidental unsupervised ingestion of acetaminophen would be managed. The AAPCC practice guideline recommends referral to an emergency department if the estimated amount ingested either is unknown or 200 mg/kg or more [6]. Repeat supratherapeutic ingestions of acetaminophen involve any pattern of multiple medication errors and ingestions over a period of greater than 8 to 24 hours. According to the AAPCC practice guideline, children less than 6 years of age should be referred to an emergency department if they have ingested 200 mg/kg or more over a single 24-hour period, 150 mg/kg or more per 24-hour period for the preceding 48 hours or 100 mg/kg or more per 24-hour period for the preceding 72 hours or longer [6]. According to experts in medical toxicology, repeated supratherapeutic ingestions of approximately 150 mg/kg/day for 2 days or more is the threshold dose needed to produce toxicity in children, although higher dosages are almost always required [6, 9].

As shown in Table 8-1, data from multiple sources including McNeil's post-marketing database, FDA's AERs database, the AAPCC, Center for Disease Control analyses of the Consumer Product Safety Commission's National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance (NEISS-CADES) and the Institute for Safe Medication Practices (ISMP) are generally consistent in identifying a number of root causes for medication errors involving acetaminophen in children.

Table 8-1. Summary of Root Causes of Medication Errors Identified by Postmarketing Databases

Root Cause	McNeil's Postmarketing Database	FDA	AAPCC	NEISS-CADES*	ISMP
Greater than recommended dose	✓ [10,11,12,**]	✓ [13,14]	✓ [5]	✓ [2]	✓ [15]
Incorrect Formulation (eg, Dosing of infants' drops at children's liquid dose)	✓ [10,11,12,**]	✓ [13,14]]	✓ [5]	✓ [2]	✓ [15]
Use of multiple acetaminophen-containing products	✓ [11, 12,**]	✓ [13,14]	✓ [5]		✓ [15]
Prescribing/dispensing error (eg, miscommunication with HCP, consumer could not verify dose on OTC label)	✓ [10,11,**]	✓ [13]	✓ [5]		✓ [15]
Administered more frequently than labeled	✓ [11,12,**]		✓ [5]	✓ [2]	✓ [15]
Administered adult product	✓ [11,12,**]	✓ [14]	✓ [5]		

Abbreviations: FDA=Food and Drug Administration; AAPCC=American Association of Poison Control Centers, NEISS-CADES= National Electronic Injury Surveillance Cooperative Adverse Drug Event Surveillance; ISMP= Institute for Safe Medication Practices

* Root Cause for Medication Errors for all products, acetaminophen 9.3% of visits annually for overdose

** See Section 8.3.1

[2] Schille SF, Shehab N, Thomas KE, et al. Medication Overdoses Leading to Emergency Department Visits Among Children. Am J Prev Med 2009;37:181-187.
[5] National Poison Data System (NPDS). 2000-2010.
[10] McNeil. Submission to FDA. April 2000.
[11] McNeil. Submission to FDA. December 2000.
[12] McNeil. Acetaminophen FDA Advisory Committee Meeting Briefing Materials. June 29-30, 2009.
[13] FDA. Briefing Document: Acetaminophen-Containing Products, Safety Issue: Hepatotoxicity August 2, 2002.
[14] FDA. Nonprescription Drug Clinical Review, Acetaminophen-Induced Hepatotoxicity. March 8, 2007.
[15] Institute for Safe Medication Practices. Available at : http://www.ismp.org. Accessed 4 April 2011.

8.3.1 Company Post-Marketing Database –Root Cause Analysis of Overdose in Children – Medication Error 2004-2010

Review of the company post-marketing adverse event database, as described in Section 8.6, identified medication error as a root cause of overdose. Of the cases reporting hepatic effects with therapeutic use (medication error), 20 cases were categorized as having moderate to severe or fatal hepatic effects. Table 8-2 lists the medication errors identified in the case review and the percentage of cases with each medication error. One case of medication error reported two root causes of overdose and is counted in 2 subcategories.

Table 8-2. Root Cause of Medication Error Resulting in Pediatric Liver Injury Following Overdose with Therapeutic Intent From Moderate to Severe, or Fatal Reports; Company Post-Marketing Database 2004-2010

Root Cause of Medication Error Leading to Overdose	n=20	%
Greater than recommended dose, unspecified	9	45%
Dosing of infants' drops at children's liquid dose[a]	7	35%
Use of multiple acetaminophen-containing products	2	10%
Prescribing/dispensing error[a]	1	5%
Administered more frequently than labeled	1	5%
Administered adult product	1	5%

[a] One case reported prescribing error and dosing of infants' drops at children's liquid dose

Of these moderate to severe or fatal medication errors, children less than 2 years of age accounted for 14 (70%) of the reports. None of these moderate to severe reports in children less than 2 years of age were fatal during this time period. Children 2 to less than 6 years of age accounted for 6 (30%) of these moderate to severe or fatal medication errors. There were no moderate to severe or fatal medication errors reported for children 6 to less than 12 years of age.

It is noteworthy that most medication errors were reported in children less than 2 years of age, an age range for which there is no dosing information on the OTC label. Adding dosing directions to the OTC single-ingredient acetaminophen label for children 6 to 23 months of age will likely reduce medication errors.

For the time period 2004-2010, over 1.6 billion dosage units of pediatric single-ingredient Tylenol products were purchased [7]. Based upon this estimated exposure, liver injury in children is very rare following medication errors.

8.4 Key Elements of McNeil's Risk Mitigation Plan Designed to Minimize Accidental Unsupervised Ingestions and Medication Errors in Children

McNeil is committed to working with FDA and other stakeholders to proactively address and reduce acetaminophen exposures and overdose in children. McNeil submitted to FDA (Docket No. FDA-2009-N-0138) a proposed risk management program aimed to reduce acetaminophen-related liver injury. McNeil's plan for infants and children targets specific root causes of unintentional pediatric acetaminophen exposures and overdoses and includes interventions aimed at minimizing accidental unsupervised ingestions and preventing medication errors.

8.4.1 Interventions Aimed at Minimizing Accidental Unsupervised Ingestions

8.4.1.1 Include Flow Restrictors in Pediatric Liquid OTC Single-Ingredient Acetaminophen Medicines

McNeil is adding flow restrictors to all of its pediatric liquid single-ingredient acetaminophen medicines to limit exposures and the magnitude of exposures in cases when children defeat child resistant features or when caregivers do not properly re-apply or re-engage them. Specifically, a flow restrictor with an accompanying syringe will be added to Infants' Tylenol Suspension to prevent children from accessing the medicine. Since the medicine will need to be accessed with an oral syringe, this innovation also has the potential to increase caregiver use of the product-specific dosing device and decrease medication errors.

For all Children's Tylenol liquid medicines, the flow restrictor has been designed to be used with a dosing cup, which is the preferred way that caregivers dose older children. Pressure needs to be applied to the plastic in order to squeeze out the medicine; this will potentially reduce children's ability to access the medicine.

8.4.1.2 Include a Child Resistant Closure on All Adult Acetaminophen-Containing Medicines

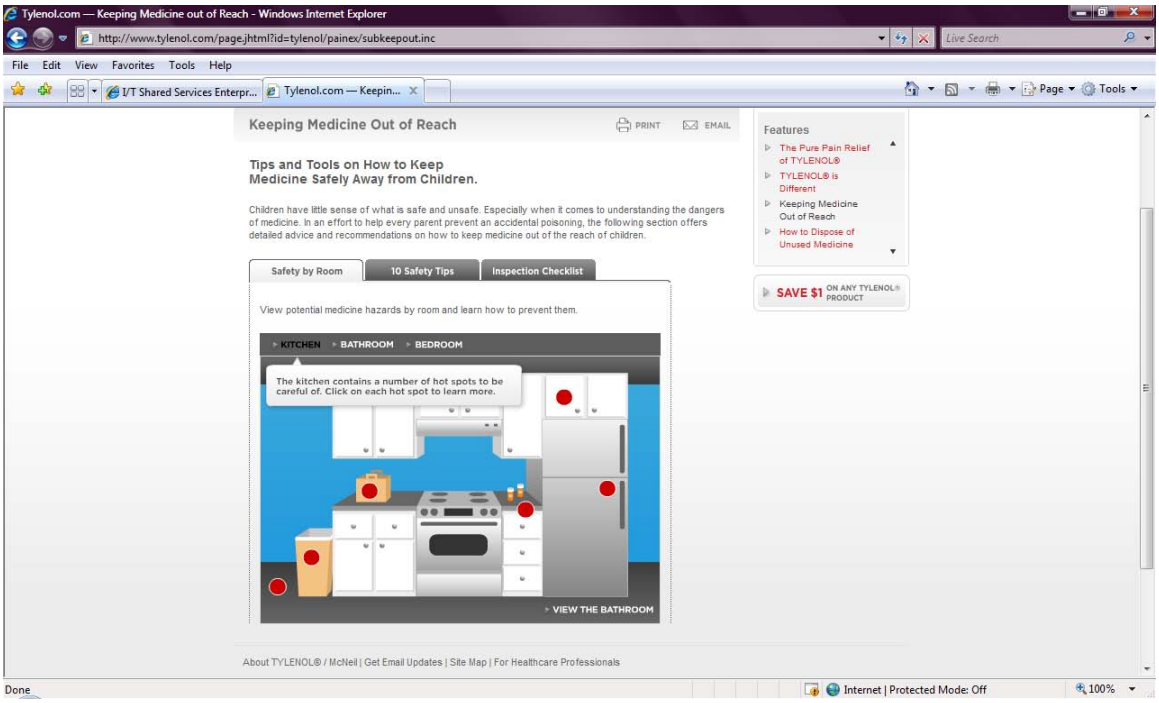
Section 4 of the Poison Prevention Packaging Act [16] allows manufacturers to market 1 single non-complying package (ie, non-child resistant) as long as the manufacturer also offers a complying package (ie, child-resistant). McNeil has changed its packaging to include a complying package on all adult acetaminophen-containing medicines.

8.4.1.3 Continue Ongoing Education of Caregivers, Healthcare Providers and Other Stakeholders about the Importance of Preventing Accidental Unsupervised Ingestions

McNeil remains committed to educating caregivers, healthcare providers and other stakeholders about the importance of preventing accidental unsupervised ingestions. The Tylenol.com website provides an interactive module titled “Keeping Medicine Out of Reach”. This module includes tips and tools on how to keep medicine safely away from children. The site also contains a downloadable inspection checklist to help caregivers perform a quick and thorough inspection of their home to help to ensure that medicine is out of reach of children.

Figure 8-1 shows an example of one of the pages from the Tylenol.com website. This page provides the consumer with the ability to explore safe and unsafe places to store medicines in an interactive demonstration of different rooms within a home.

Figure 8-1:Tylenol.com: Keeping Medicine Out of Reach



McNeil is also currently participating in the PROTECT initiative, which is an innovative collaboration bringing together public health agencies, private sector companies, professional organizations, consumer/patient advocates, and academic and health literacy experts to develop strategies to keep children safe from unintentional medication overdoses.

8.4.2 Interventions Aimed at Preventing Medication Errors

Data from multiple sources confirm that medication errors, although much less common than accidental unsupervised ingestions, result in acetaminophen overdose. Commonly identified reasons for pediatric medication errors with acetaminophen include: dosing of infants' drops at children's liquid dose, use of multiple acetaminophen-containing medicines, administration of adult medicine to a child, administering greater than the recommended dose, administering more frequently than recommended, and prescribing or dispensing errors.

8.4.2.1 Addition of Dosing Directions for Children 6 to 23 Months on OTC Label for Single-Ingredient Acetaminophen Medicines

Adding dosing information for children 6 to 23 months of age on the OTC label will likely decrease a preventable root cause of acetaminophen dosing errors and decrease consumer confusion. McNeil proposes to add dosing directions on the OTC label of our acetaminophen infants' product for children aged 6 to 23 months of age. These new dosing directions will be highlighted on the package. McNeil believes that the inclusion of dosing instructions for children less than 2 years of age will likely reduce pediatric medication errors leading to acetaminophen overdose.

8.4.2.2 Transition to Single Concentration of 160 mg/5 mL for All OTC Single-Ingredient Pediatric Liquid Acetaminophen Medicines

McNeil has worked closely with the Consumer Healthcare Products Association (CHPA) and member companies to transition to a single concentration of 160 mg acetaminophen per 5 milliliters for all OTC single-ingredient pediatric liquid acetaminophen medicines. The concentrated (80 mg/0.8 mL) drops will be phased out and only the single concentration of 160 mg/5 mL will be available.

8.4.2.3 Standardize Dosing Abbreviations and Volumetric Measures in Dosing Directions for All OTC Pediatric Liquid Acetaminophen Medicines

As part of multiple stakeholder efforts to help prevent accidental, unsupervised medication ingestions and overdoses in children, the members of CHPA participated in developing voluntary guidelines. These guidelines suggest ways to improve the consistency and standard format of volumetric measures within the dosing directions on the outer packaging and immediate container label, as well as on the dosing device for OTC oral liquid drug products with dosing directions for children, defined as ≤12 years of age [17]. McNeil continues to standardize dosing abbreviations and volumetric

measures in dosing directions for OTC pediatric liquid acetaminophen-medicines that we market.

8.4.2.4 Continue to Include an In-pack Calibrated Dosing Device for All OTC Single-Ingredient Acetaminophen Pediatric Liquid Medicines

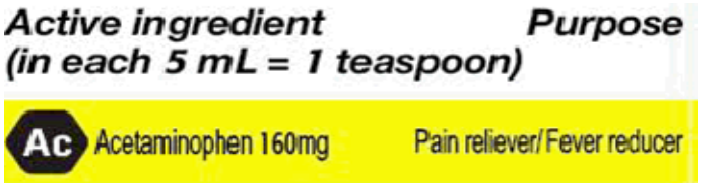
McNeil has included an in-pack calibrated dosing device for all OTC single-ingredient acetaminophen pediatric liquid medicines since the early 1990s and has also established a requirement in the "Directions" section of the OTC label to use the in-pack measuring device. This serves as a reminder to caregivers of the importance of always using the dosing device that accompanies the medicine.

8.4.2.5 Develop, Validate and Align Stakeholders to an Acetaminophen Ingredient Icon for Inclusion in Drug Facts for all OTC Acetaminophen-Containing Medicines and on all Pharmacy Generated Prescription Labels for Prescription Acetaminophen-Containing Medicines

McNeil is working with the OTC industry to test and implement optimal methods (eg, icons, pictograms) to communicate acetaminophen as an ingredient in OTC and prescription medicines. Icons and pictograms have been shown to direct attention to health information [18], help consumers understand concepts, or convey key messages about using the medicine [18, 19, 20, 21, 22, 23, 24]. A graphical symbol (icon) may help consumers recognize acetaminophen in multiple products, and help minimize simultaneous use of multiple acetaminophen-containing medicines (eg, OTC and/or prescription).

Figure 8-2 provides an example of an experimental acetaminophen icon on a single-ingredient acetaminophen pediatric liquid medicine label. The purpose of the icon is to communicate acetaminophen as an ingredient.

Figure 8-2. Example of an Acetaminophen Icon



8.4.2.6 Continue Education of Caregivers, Healthcare Providers and Other Stakeholders about the Importance of Preventing Medication Errors in Children

McNeil continues to provide consumers and healthcare providers information about the responsible use of children's medicines. Figure 8-3 provides an example of a tear sheet that McNeil created and distributed to healthcare providers in 2008-2009 to educate caregivers on the proper use of OTC pain relievers. This information included important messaging such as: always reading and following the label instructions, never giving adult medicine to children, always using the dosing device that comes packaged with the medicine, and reminding parents and caregivers to always check the ingredients of the medicines they are administering to make sure they do not contain any of the same ingredients, and the importance of keeping medicine locked and out of the reach of children.

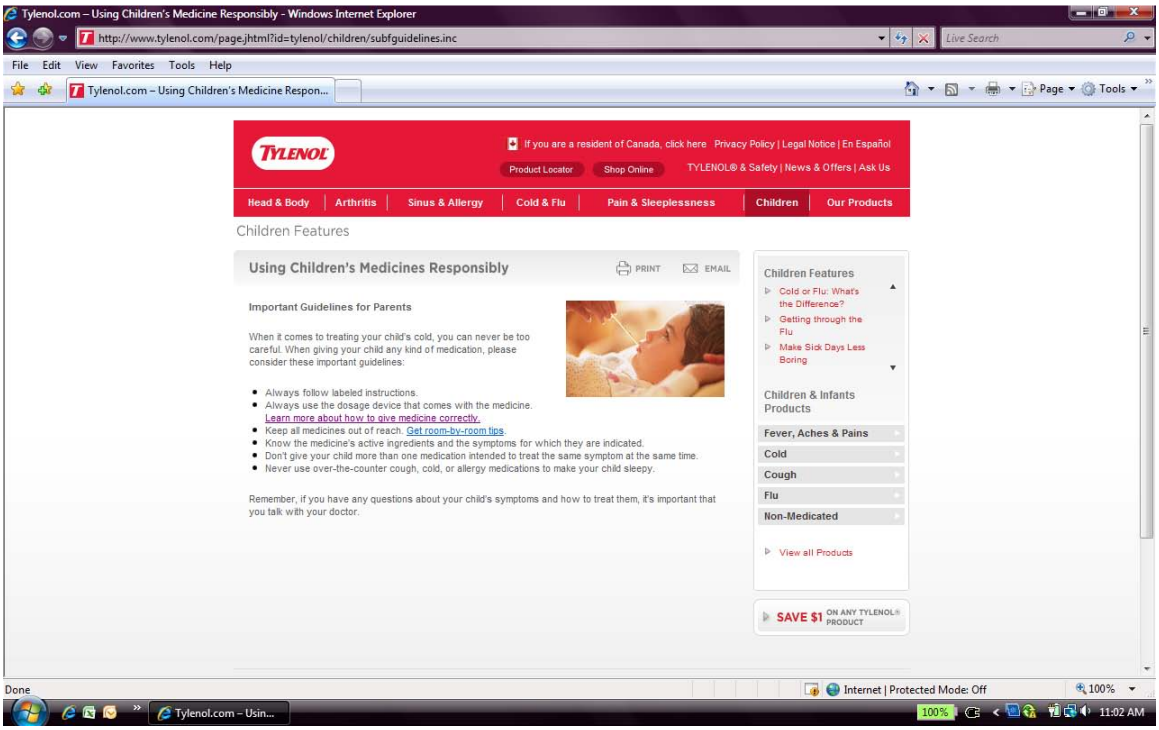
Figure 8-3 Proper Use of Over-the-Counter Pain Relievers

The Tylenol.com website also currently provides a variety of information on how to use children's medicines responsibly including a guideline for parents and caregivers to

consider when administering medicine to their children. These guidelines are presented in Figure 8-4 and include the following key messages:

- Always follow labeled instructions.
- Always use the dosage device that comes with the medicine.
- Keep all medicines out of reach.
- Know the medicine's active ingredients and the symptoms for which they are indicated.
- Don't give your child more than one medication intended to treat the same symptom at the same time.
- Never use over-the-counter cough, cold, or allergy medications to make your child sleepy.

Figure 8-4 Tylenol.com: Using Children's Medicines Responsibly



8.4.3 McNeil Efforts on Surveillance and Education

To help reduce the incidence of medication errors and accidental unsupervised ingestions of acetaminophen products, McNeil will partner with stakeholders to evaluate and test enhanced education messages (eg, "Don't use adult medicines in children" and "Don't give more than the recommended dose" and "Keep medicines out of the reach of children").

It is important that the impact from changes to pediatric packaging, labeling, and education be measured closely. Where data gaps exist, McNeil is committed to

supporting scientific research and surveillance designed to provide additional data and enhance our understanding of acetaminophen overdose and liver injury. Specifically, McNeil will work collaboratively with FDA, public health authorities, other manufacturers and healthcare providers to develop specific data collection tools in order to better understand caregiver behaviors and other potential risk factors that may lead to acetaminophen overdose and liver injury.

Existing surveillance systems should be augmented to seek out cases and systematically gather and record information in a transparent fashion. These data collection systems must use clear and consistent definitions to accurately define and collect key information for evaluating root causes, such as patient characteristics, products involved, intent and indications for use. It is also important that with each case those collecting the data attempt to understand, as best they can, the actual dose ingested or administered and the duration of use.

McNeil will work with stakeholders to set goals for measuring the impact of the proposed interventions on patient understanding, medicating behaviors and acetaminophen overdose and liver injury and will work to establish appropriate measures and metrics to evaluate the impact of changes. Some metrics McNeil is proposing include: establishing a baseline and tracking the number of reports documented by poison centers, emergency departments, and in our company post-marketing safety database. Changes in both the number of cases, the magnitude of exposures, and the seriousness of the adverse events will be evaluated.

McNeil will participate with industry in an infants' acetaminophen concentration transition plan. In addition, McNeil will lead an education program targeted to healthcare professionals and caregivers of children ages for which the pediatric product is intended. Education will serve to raise awareness that there will be a new concentration of infants' acetaminophen products available and therefore there will be new dosing directions. Additionally, healthcare providers and caregivers will be urged to be particularly diligent during the transition period where infants' products with multiple concentrations will be available on store shelves as well as in medicine cabinets because using the new dosing directions with the older concentration could result in overdose.

McNeil's education program will target healthcare professionals and caregivers through multiple channels including:

- communication through professional organizations
- direct mail and email notifications
- at-shelf communications

- a phone line staffed by healthcare professionals that can provide dosing directions to caregivers

8.5 Conclusions

All of these elements described in McNeil's Risk Mitigation Plan will continue to help address the root causes of acetaminophen overdose in children. These root causes include caregivers not following dosing directions, caregivers administering multiple acetaminophen-containing medicines at once, accidental unsupervised ingestions, not properly using pediatric formulations, and administering adult medicines to children.

- Data from multiple sources confirm that accidental unsupervised ingestions are the most common root cause of unintentional acetaminophen exposures in children.

- Data from multiple sources confirm that medication errors, although much less common than accidental unsupervised ingestions, result in acetaminophen overdose in children.

- Liver injury in children is very rare following accidental unsupervised ingestions or medication errors.

- McNeil is committed to working with FDA and other stakeholders to proactively address and reduce unintentional acetaminophen exposures and overdose in children. The Risk Mitigation Plan is based upon and targeted to specific root causes of unintentional pediatric acetaminophen exposures and overdoses and includes interventions aimed at minimizing accidental unsupervised ingestions and preventing medication errors.

- The addition of dosing directions to the OTC single-ingredient acetaminophen label for children 6 to 23 months of age will likely reduce medication errors.

8.6 Supportive Methodology for Review of Safety Data from the McNeil Post-Marketing Database

The company post-marketing safety database for acetaminophen was queried for the 7 year period from January 1, 2004 through December 31, 2010 for pediatric cases (age less than twelve years) from the United States that had a MedDRA Preferred Term in the Standard MedDRA Query (SMQ) for Possible Drug Related Hepatic Disorders – Comprehensive Search for single-ingredient acetaminophen products were collected. The cases were manually reviewed by McNeil and categorized according to intent (accidental unsupervised ingestion, therapeutic, self-harm/malicious), severity of clinical hepatic effect (mild, moderate to severe, fatal), and dose (overdose, therapeutic dose, unknown) in order to better understand potential root causes of overdose for these cases. Mild hepatic effects were defined as an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) less than 500 IU/L without evidence of hepatic failure or dysfunction or if liver tenderness or pain was reported. If liver enzymes were not reported, the report was categorized as mild if it described “elevated enzymes”, “hepatitis”, “abnormal liver function tests”, or “liver problems”. Moderate to severe hepatic effects were defined as an AST or ALT greater than 500 IU/L or if the report described “liver damage”, elevated international normalized ratio without pharmacologic anticoagulation, elevated bilirubin or jaundice, biopsy with evidence of centrilobular necrosis, acute liver failure, a liver transplant, hepatic encephalopathy, or multi-organ failure.

For this review, any case in which it could be verified that the event did not occur within the 2004 to 2010 timeframe was excluded and duplicate cases were carefully identified.

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