OTC Acetaminophen Products: Use in Children

Advisory Committee Meeting

May 17, 2011

M. Scott Furness, Ph.D.
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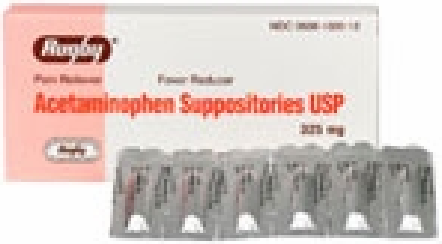
Office of Drug Evaluation IV

What are Pediatric OTC Drugs Containing Acetaminophen?



New Drug Application (NDA)

OTC Monograph

What is the Key Question?

- Are the existing dosing directions and age breakdowns sufficient to appropriately administer OTC acetaminophen containing drug products to children?

McNeil Citizen Petition

- Physicians frequently recommend to consumers the use of pediatric acetaminophen in children less than two years of age.
- The firm developed dosing schedules designed to closely correlate with the administration of acetaminophen in the dose range of 10-15 mg/kg of body weight per single dose.
  - Were made available to health care professionals through the Physician's Desk Reference (PDR) and through other professional materials.

McNeil Citizen Petition

- Action Requested: Amend the current proposed regulation
  - to expand the age groups for OTC consumer dosing instructions to include children 2 months to less than 2 years of age.
  - to include age- and weight-based dosing for children less than 12 years of age.

- Current proposed regulation affords the following directions:
  - Children < age 2: No dosing instructions on the label. Only states "Consult a doctor"
  - Children 2-12: Age-based dosing

Agenda of the Meeting

- Presentations
  - FDA and FDA's Invited Speaker
    - Regulatory History
    - Pharmacokinetics
    - Medication Errors
    - Safety
    - Efficacy
    - Extrapolation
    - Utilization Patterns
    - Epidemiology
  - Industry
- Open Public Hearing
- Discussion
- Voting

Questions for the Advisory Committee

1. Should weight-based dosing directions be added to the existing age-based labeled dosing directions for children ages 2-12?
   a. If the answer is yes, how should dosing directions be written using incremental increases in dosing based on age and weight?
2. Do the pharmacokinetic (PK), safety, and efficacy data support the addition of new labeled dosing directions corresponding to a 10-15 mg/kg dose for children 6 months to 2 years of age?
   a. If the answer is yes, should the new labeling include antipyretic and analgesic claims?

Questions for the Advisory Committee

3. In what ways can the labeling, packaging, and the container/closure system be improved such that medication errors can be minimized?
4. Restricting liquid formulations to a single concentration was a recommended intervention discussed at a recent (2009) advisory committee meeting addressing acetaminophen safety. Should the agency consider similar measures for pediatric acetaminophen-containing solid oral dosage forms?

Thank You

Back-Up Slides Shown

McNeil's Proposed Pediatric Dosing

Ages 6 months through 11 years

Source: 1999 Citizen Petition and 2010 update

Weight (pounds)	Age	Dose (mg)
12-17 lbs	6-11 mos	80 mg
18-23 lbs	12-23 mos	120 mg
24-35 lbs	2-3 yrs	160 mg
36-47 lbs	4-5 yrs	240 mg
48-59 lbs	6-8 yrs	320 mg
60-71 lbs	9-10 yrs	400 mg
72-95 lbs	11 yrs	480 mg

Pediatric Dosing
Ages 2 through 11 years

McNeil		Alternate		Dose
Weight	Age	Weight	Age	mg
24-35 lb	2-3 y	24-35 lb	2-3 y	160
36-47 lb	4-5 y	36-52 lb	4-5 y	240
48-59 lb	6-8 y	**53-70** lb	6-8 y	320
60-71 lb	9-10 y	**71-88** lb	9-10 y	400
72-95 lb	11 y	**89-106** lb	11 y	480

Pediatric Dosing
Ages 6 through 23 months

McNeil		Alternate		Dose
Weight	Age	Weight	Age	mg
12-17 lb	6-11 m	12-14 lb	6-7 m	80
		15-17 lb	8-11 m	100
18-23 lb	12-23 m	18-20 lb	12-18 m	120
		21-24 lb	19-23 m	140

Regulatory History of Pediatric Acetaminophen Dosing

Nonprescription Drugs Advisory Committee
Pediatric Advisory Committee
May 17-18, 2011

Kathleen M. Phelan, R.Ph.
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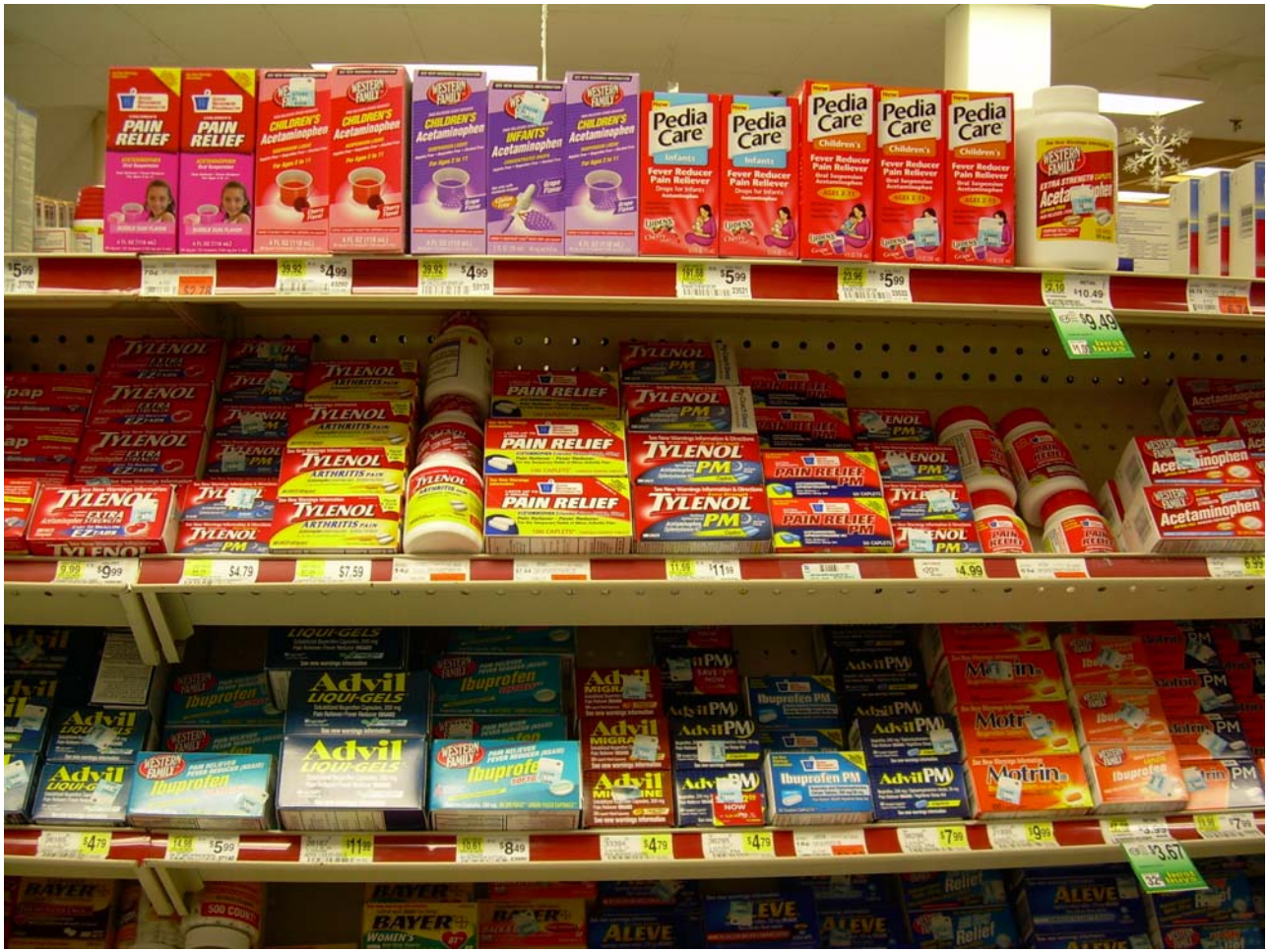
Center for Drug Evaluation and Research
Food and Drug Administration

Retail Pharmacy Shelf



Outline

- Regulation of over-the-counter (OTC) drug products
- Available OTC acetaminophen products
- Regulatory history of acetaminophen (dosing for children under 12 years of age)
- Previous advisory committee meetings

Two Regulatory Pathways

New Drug Application (NDA)

OTC Drug Monograph

Regulation of OTC Drugs

New Drug Application (NDA)	OTC Drug Review (Monograph)
Product (formulation) specific	Active ingredient specific
Pre-marketing approval	No pre-marketing approval
Confidential filing and review	Public notice and comment rulemaking

Why submit an NDA?

- Monograph limits product options
  - GRAS/E active ingredients
  - Specified indications, populations, dosing, route of administration, labeled warnings…
  - Time-release products not suitable

Regulation of OTC Drugs

- 1938 Food, Drug, and Cosmetic Act
  - Drugs must be safe to use
  - New Drug Application (NDA)
- 1962 Drug Amendments Act
  - Drugs must be effective
  - Efficacy review of drugs approved since 1938
  - 25% of 420 OTC drugs found effective
- 1972 OTC Drug Review = Monograph process Federal Register 37 (Jan 5, 1972): 85-89.

OTC Drug Review (Monograph Process)
1972 Federal Register notice

26 therapeutic categories

Acceptable supporting data

Review of data

- Advisory Review Panels
- Panel reports: conditions under which drugs are generally recognized as safe (GRAS) and effective (GRAE) and not misbranded

Public comment and rulemaking process

OTC Drug Review (Monograph Process)

Advisory Review Panel

↓

Advance **N**otice of **P**roposed **R**ulemaking

ANPR

Comment period

↓

Tentative **F**inal **M**onograph (Proposed Rule)

TFM

Comment period

↓

Final **M**onograph (Final Rule)

FM

Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) Drug Products

Advisory Review Panel

↓

Advance **N**otice of **P**roposed **R**ulemaking

1977 ANPR

Comment period

↓

Tentative Final Monograph (Proposed Rule)

1988 TFM

Comment period

↓

Final **M**onograph (Final Rule)

FM

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- Regulation of over-the-counter (OTC) drug products
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Available OTC Acetaminophen Products

NDA Rectal Suppositories	
Strength	Labeled Ages
80 mg	6-36 months
120 mg	3-6 years
325 mg	≥ 6 years
650 mg	≥ 12 years

Available OTC Acetaminophen Products
(continued)

NDA Oral Extended-release Tablets	
Strength	Labeled Ages
650 mg	≥ 12 years

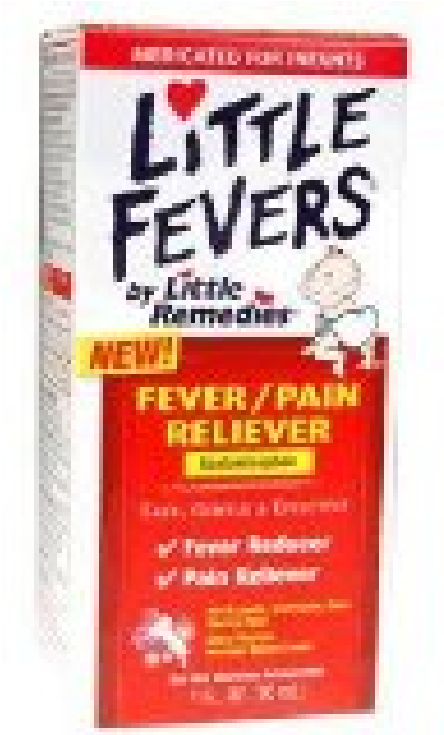
Available OTC Acetaminophen Products
(continued)

Monograph Oral Immediate-release Solid	
Strength	Labeled Ages
80 mg	≥ 2 years
160 mg	≥ 6 years
325 mg	≥ 6 years
500 mg	≥ 12 years

Available OTC Acetaminophen Products
(continued)

Monograph Oral Immediate-release Liquid	
Concentration	Labeled Ages
80 mg/0.8 mL	2-3 years
80 mg/1 mL	2-5 years
160 mg/5 mL	2-11 years
500 mg/15 mL	≥ 12 years

Confusing?



80 mg / 1 mL
2 to 5 years

80 mg / 0.8 mL
2 to 3 years

160 mg / 5 mL
2 to 11 years

Outline

- Regulation of over-the-counter (OTC) drug products
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Acetaminophen Regulatory History

	Approved under NDA for prescription use
1955	Exemption from prescription (OTC) with dosing for ages 6 years and older
1959	Exemption from prescription (OTC) with dosing for ages 3 years and older
1972	Oral, immediate-release acetaminophen moves from NDA to monograph
1977	ANPR - dosing for ages 2 years and older
1988	TFM - dosing for ages 2 years and older

Acetaminophen Regulatory History ANPR 1977 → TFM 1988

Public Comments: Allow pediatric dosing by weight instead of or in addition to age

FDA Response:

- Age is acceptable basis for dosing - doses correlate with doses calculated using BSA.
- FDA will consider use of weight-based dosing for all OTC products in future rulemaking

Federal Register 53 (Nov 16, 1988): 46204-46260.

Acetaminophen Regulatory History Dosing in IAAA TFM

(every 4 hours, not to exceed 5 doses/24 hours)

2 to < 4 years	160 mg
4 to < 6 years	240 mg
6 to < 9 years	325 mg
9 to < 11 years	325 to 406.3 mg
11 to < 12 years	325 to 487.5 mg
≥ 12 years (adult)	325 to 650 mg

Federal Register 53 (Nov 16, 1988): 46204-46260.

Outline

- Regulation of over-the-counter (OTC) drug products
- Available acetaminophen products
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Previous Advisory Committee Meetings Topics

1995 Pediatric Dosing of OTC Drugs

1997 Pediatric Dosing and Labeling of OTC Analgesic / Antipyretic Drugs

2002 Unintentional Acetaminophen Overdose

2009 Acetaminophen-Induced Liver Injury

Previous Advisory Committee Meetings Recommendations

- Dose children by weight
- Include dosing by age (weight unknown)
- Base pediatric dosing on data
- Allow only one concentration of pediatric liquid acetaminophen on the OTC market
- Label dosing to 2 months old but warn that child < 6 months must see doctor for fever
  - *FDA decided OTC label can be ≥ 6 months*

1999 McNeil Consumer Healthcare Citizen Petition

- Request to label OTC acetaminophen for ages ≥ 2 months
  - Updated petition in 2010 to request OTC labeling for ages ≥ 6 months
- Propose age and weight-based doses of 10-15 mg/kg every 4 hours for ages 0 to 12 years (Temple. Ped Pharmacol 1983)
- Proposed dosing in PDR since developed

TYLENOL® Professional Dosing Information for Infants & Children

Note: If possible, use weight to dose, otherwise use age. To arrive at the correct dose, weigh your child before giving TYLENOL®. **A healthcare professional should be consulted for dosing in children under the age of two years.**

Feel better, TYLENOL® ACETAMINOPHEN

Always ask your healthcare professional which product is right for your child.

	Your child's weight and age								
Age	0-3 mos	4-11 mos	12-23 mos	2-3 yrs	4-5 yrs	6-8 yrs	9-10 yrs	11 yrs	12 yrs
Weight	6-11 lbs	12-17 lbs	18-23 lbs	24-35 lbs	36-47 lbs	48-59 lbs	60-71 lbs	72-95 lbs	95 lbs & over
Concentrated TYLENOL® Infants' Drops *Cherry, Grape & Cherry dye-free flavors* **Active Ingredient:** Acetaminophen 80mg (in each 0.8mL) Use only as directed.	0.4mL	0.8mL	1.2mL (0.8mL + 0.4mL)	1.6mL (0.8mL + 0.8mL)	–	–	–	–	–
Children's TYLENOL® Suspension *Cherry Blast, Very Berry Strawberry, Bubblegum Yum, Grape Splash & Cherry dye-free flavors* **Active Ingredient:** Acetaminophen 160mg (in each 5mL or 1 tsp) Use only as directed.	–	–	–	1 tsp or 5mL	1 1/2 tsp or 7.5mL	2 tsp or 10mL	2 1/2 tsp or 12.5mL	3 tsp or 15mL	–
Children's TYLENOL® Meltaway Tablets *Bubblegum Burst, Wacky Watermelon & Grape Punch flavors* **Active Ingredient:** Acetaminophen 80mg (in each tablet) Use only as directed.	–	–	–	2 tablets	3 tablets	4 tablets	5 tablets	6 tablets	–
Jr. TYLENOL® Meltaway Tablets *Bubblegum Burst & Grape Punch flavors* **Active Ingredient:** Acetaminophen 160mg (in each tablet) Use only as directed.	–	–	–	–	–	2 tablets	2 1/2 tablets	3 tablets	4 tablets

tsp = teaspoon*

Take every 4 hours as needed. Do not exceed more than 5 doses in 24 hours.

Important Instructions for Proper Use

- **Read and follow the label instructions on all TYLENOL® products**
  - Take every 4 hours as needed
  - Do not exceed more than 5 doses in 24 hours
- **Do NOT use with any other product containing acetaminophen**
- **Keep all medicines out of the reach of children**
- **Do NOT administer adult medicines to children**
- ***Use only the dosing device that comes with a specific product**
- Concentrated TYLENOL® Infants' Drops are more concentrated than Children's TYLENOL® Liquids. The Concentrated Infants' Drops have been specifically designed for use with enclosed dropper.
- Children's TYLENOL® Liquids are less concentrated than Concentrated TYLENOL® Infants' Drops. The Children's TYLENOL® Liquids have been specifically designed for use with the enclosed measuring cup.
- Children's TYLENOL® Meltaway Tablets are not the same concentration as Jr. Strength TYLENOL® Meltaway Tablets. Jr. TYLENOL® Meltaway Tablets contain 160mg of acetaminophen while Children's TYLENOL® Meltaway Tablets contain 80mg of acetaminophen.
- **If you have any questions, contact your healthcare professional or call 1-877-895-3665**

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TABLE 1
Children's ‹Tylenol›® Dosing Chart

AGE GROUP		0–3 mos	4–11 mos	12–23 mos	2–3 yrs	4–5 yrs	6–8 yrs	9–10 yrs	11 yrs	12 yrs	
WEIGHT	(if possible use weight to dose; otherwise use age)	6–11 lbs	12–17 lbs	18–23 lbs	24–35 lbs	36–47 lbs	48–59 lbs	60–71 lbs	72–95 lbs	96 lbs and over	
PRODUCT FORM	INGREDIENTS	Dose to be administered based on weight or age †									Maximum doses/24 hrs
Infants' Drops	In each (0.8 mL)										
Concentrated ‹Tylenol› Infants' Drops	Acetaminophen 80 mg	(0.4 mL) *	(0.8 mL) *	1.2 mL (0.8 + 0.4 mL) *	1.6 mL (0.8 + 0.8 mL)	—	—	—	—	—	5 times in 24 hrs

†All products may be dosed every 4 hours, if needed.

*Under 2 years (under 24 lbs), consult a doctor.

Update

- Advisory committee meetings
- Children in clinical trials
  - 2002 Best Pharmaceuticals for Children Act (BPCA)
    - Reauthorized a provision originally contained in the 1997 Food and Drug Administration Modernization Act (FDAMA)
  - 2003 Pediatric Research Equity Act (PREA)

Regulatory History of Pediatric Acetaminophen Dosing

http://www.boxvox.net/2010/07/tylenol-childrens-elixir.html

Clinical Pharmacology Findings of Acetaminophen in Pediatric Patients

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Office of Clinical Pharmacology
Center of Drug Evaluation and Research
Food and Drug Administration

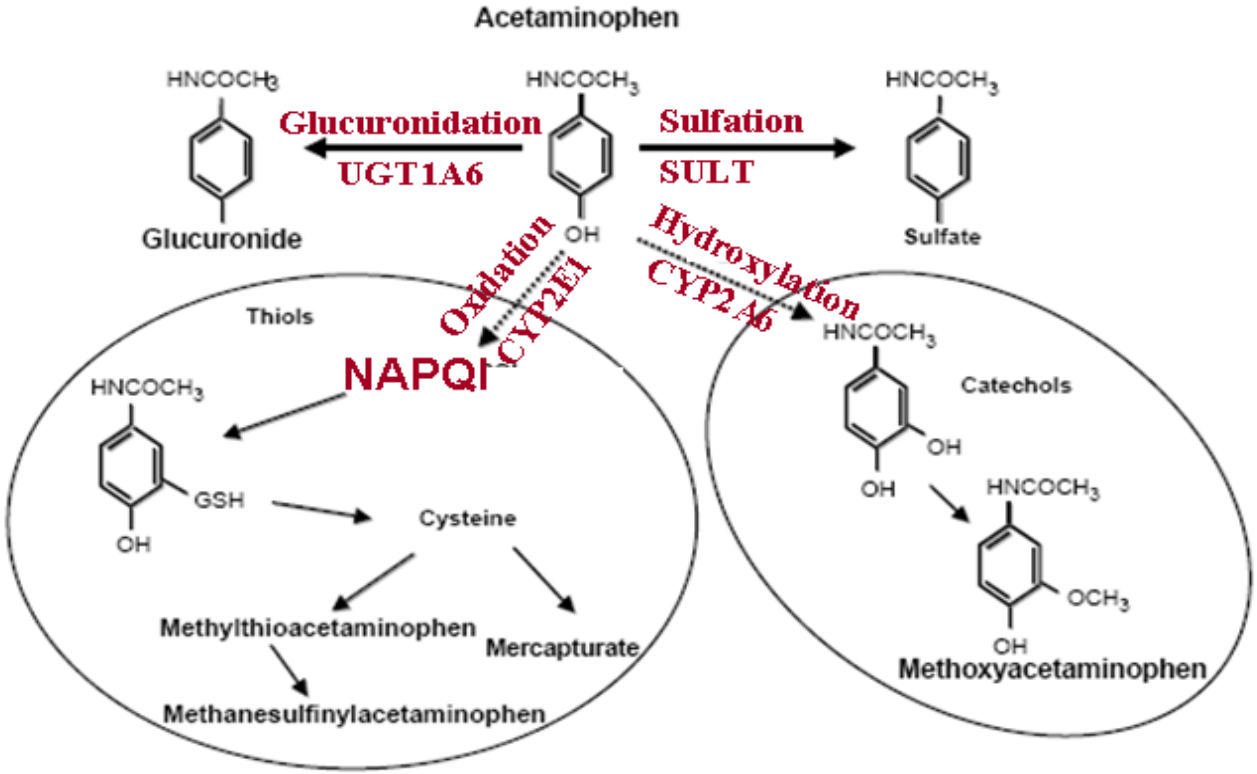
Outline

- Acetaminophen metabolism and the maturation of metabolic pathways
- Acetaminophen pharmacokinetics in pediatric patients
- Dose response relationship for acetaminophen fever reduction in pediatric patients

Outline

- Acetaminophen metabolism and the maturation of metabolic pathways
- Acetaminophen PK in pediatric patients
- Dose response relationship for acetaminophen fever reduction in pediatric patients

Metabolic Pathways in Humans



Gelotte, 2007

- **All metabolites are inactive.**
- **NAPQI, N-acetyl-p-benzo-quinone imine, may cause liver toxicity after a massive acute overdose.**
- **Hydroxylation pathway of no clinical importance.**

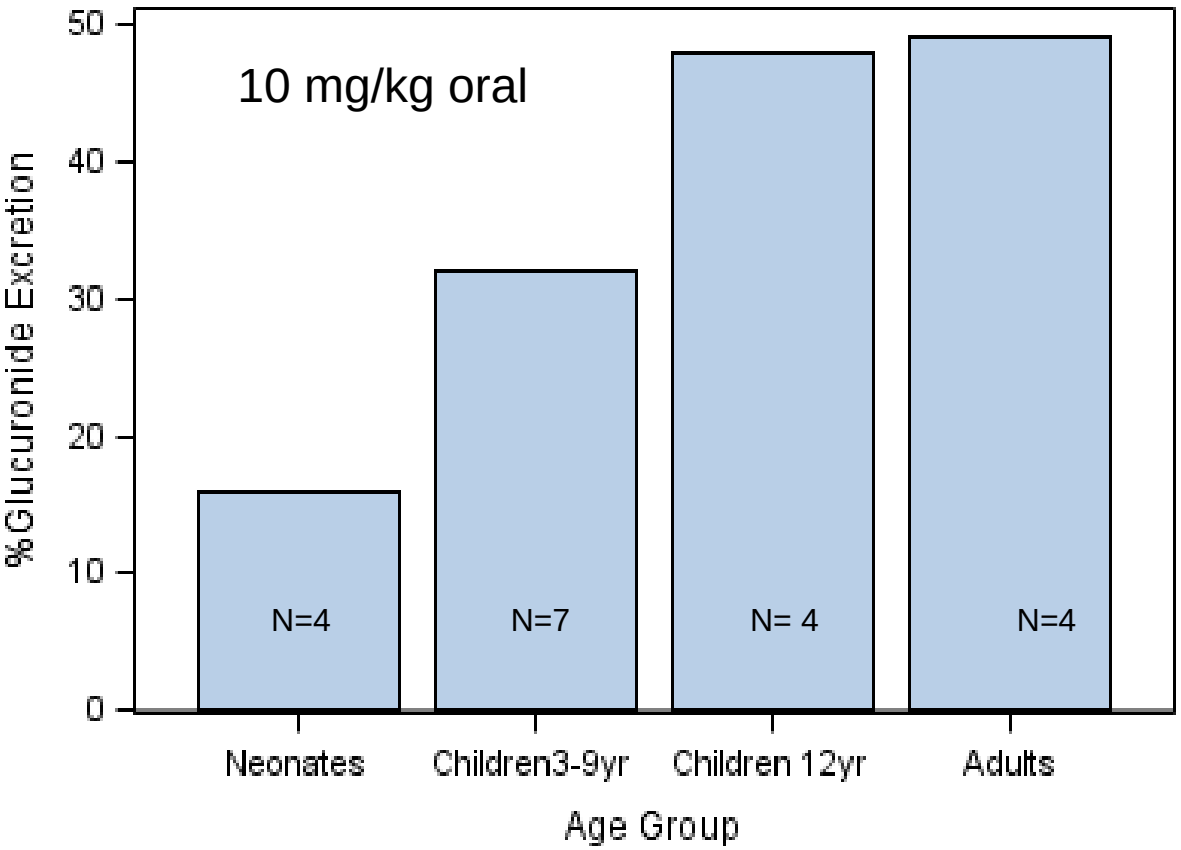
Metabolic Pathways in Adults

- Relative contribution of each metabolic pathway:
  - Glucuronidation: 50-60%
  - Sulfation: 25-30%
  - Oxidation: <10%
  - Hydroxylation: <5%

Metabolic Pathways in Pediatrics

- Contributing enzymes mature at different ages
  - SULT1A1 (sulfation) mature at birth
  - UGT1A6 (glucuronidation) and CYP2E1 (oxidation) immature in younger pediatrics
- Relative contribution of each metabolic pathway changes with age

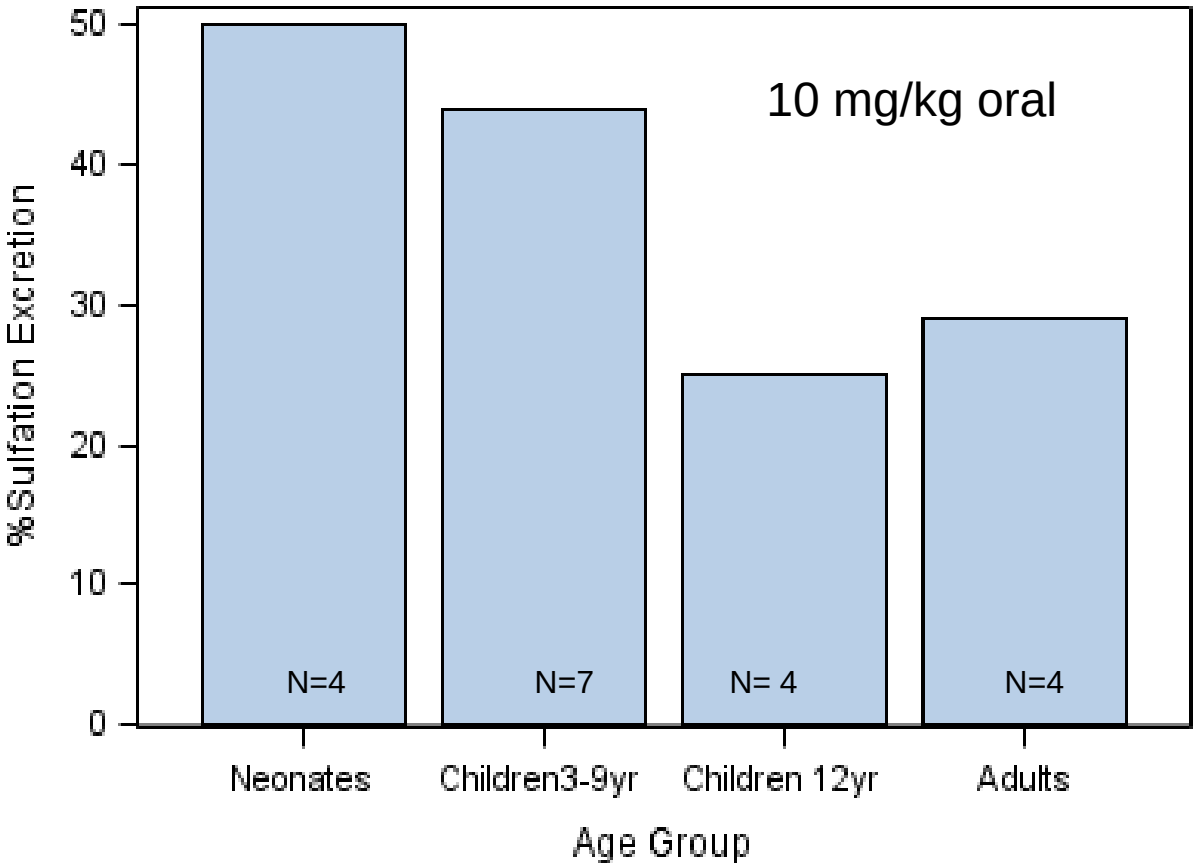
Pediatrics: Glucuronidation



Lower % excreted in the urine as glucuronide conjugate in younger pediatrics patients

Miller 1976

Pediatrics: Sulfation



Higher % excreted in the urine as sulfate conjugate in younger pediatrics patients

Miller 1976

Pediatrics: Oxidation

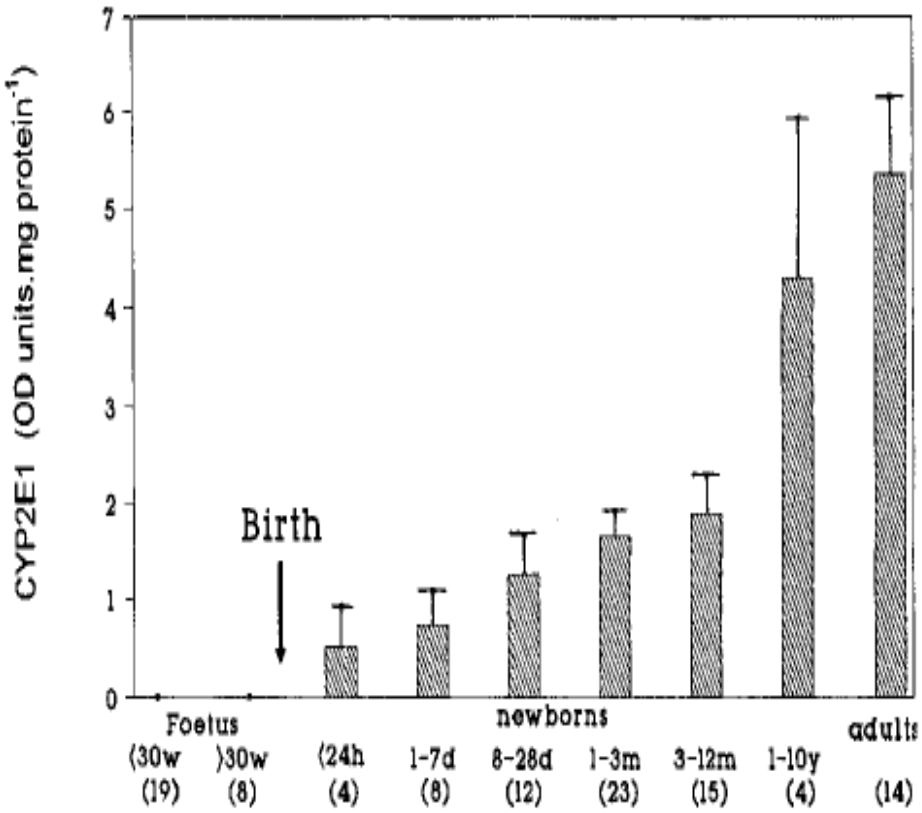


Fig. 1. Age-related variations of CYP2E1 protein in the human liver.

--Oxidation mainly mediated by CYP2E1

-CYP2E1 protein absent in the fetal liver

- CYP2E1 level gradually increases during the first year of life and approaches adult level between 1 to 10 years.

Vieira, 1996

Summary of Metabolic Pathways

- Sulfation predominates acetaminophen metabolism in the younger pediatrics.
- Expression of CYP2E1 responsible for oxidation pathway is less in neonates and infants as compared to older pediatrics.

Outline

- Acetaminophen metabolism and the maturation of metabolic pathways
- Acetaminophen PK in pediatric patients
- Dose response relationship for acetaminophen fever reduction in pediatric patients

Acetaminophen PK

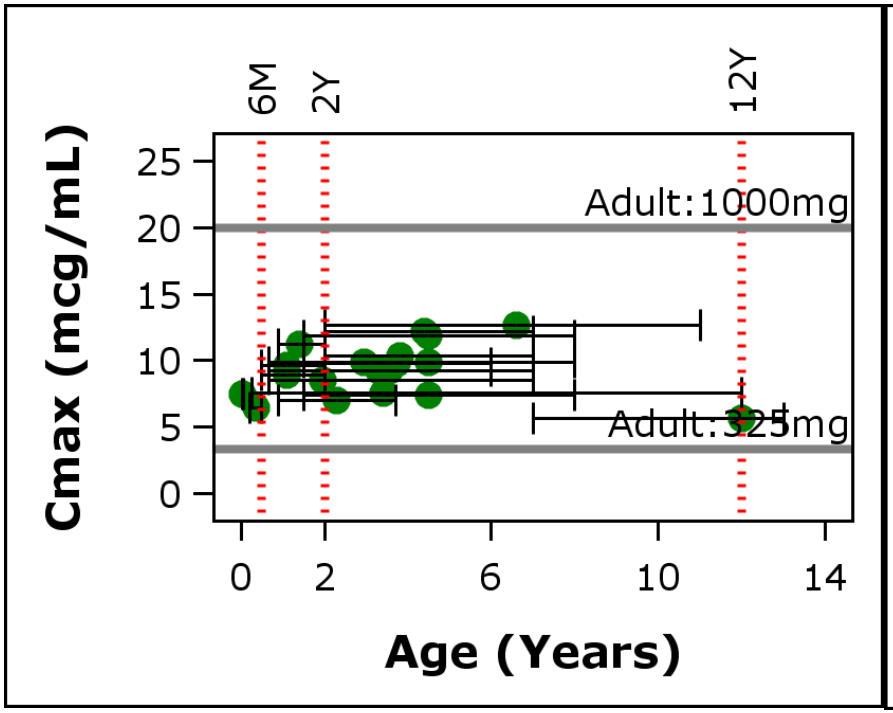
- Review focused on:
  - Pediatric patients <12 years of age
  - Oral dose
  - Single dose or multiple doses
  - PK measurements with Tmax, T1/2, AUC and/or Cmax

Acetaminophen PK

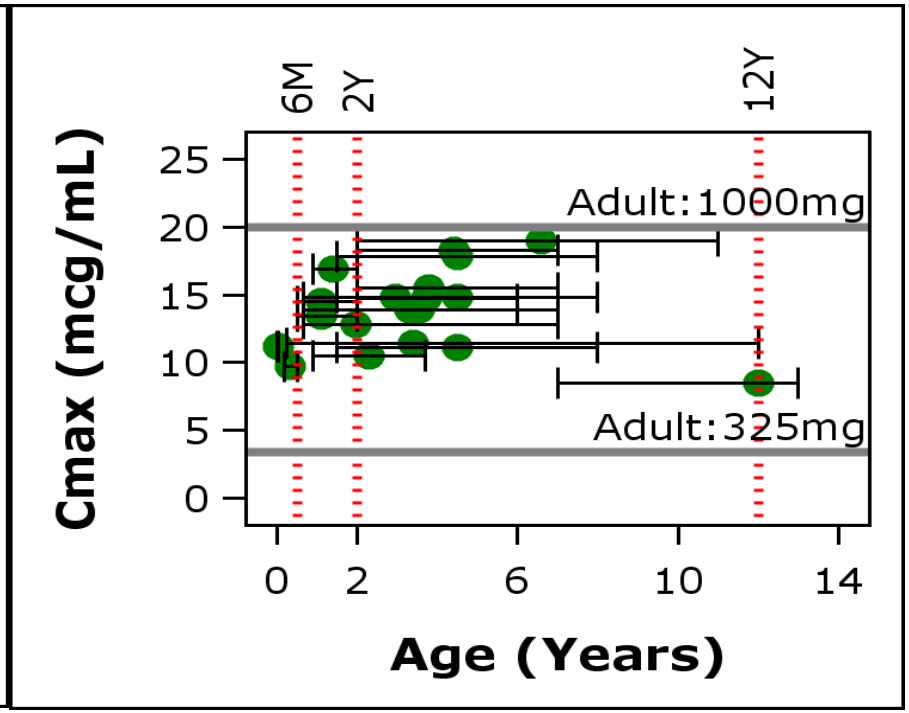
- Results:
  - Identified 8 publications and 2 in-house studies from McNeil
  - N=208
  - Age range: neonates to 13 years
  - Oral dose range: 5 to 30 mg/kg
  - Mean T1/2: 1.4 to 3.1 h
  - Mean Tmax: 0.5 to 1.8 h
  - Minimum accumulation after multiple doses

Acetaminophen PK: Cmax

Normalized to 10 mg/kg



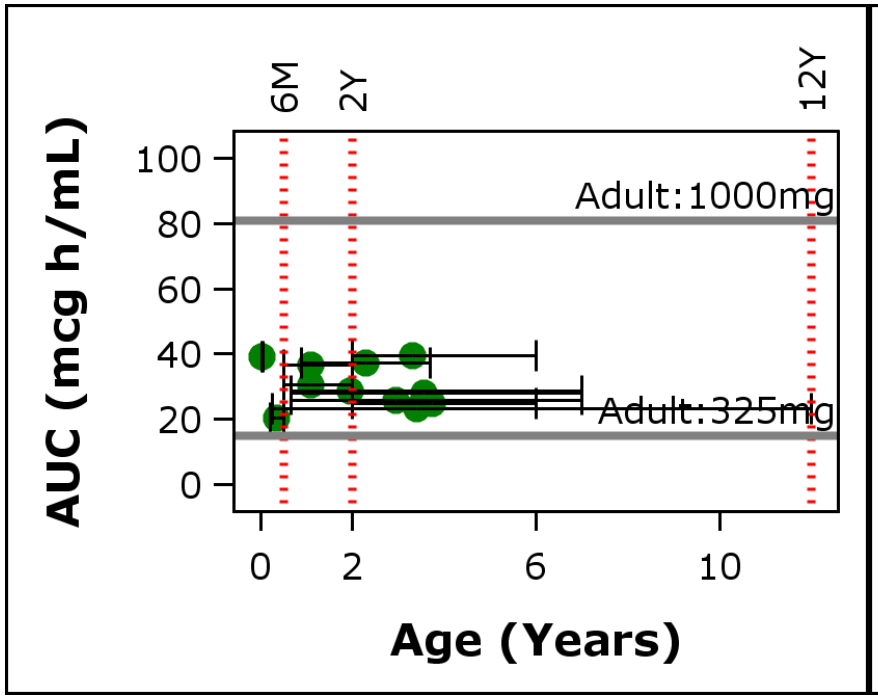
Normalized to 15 mg/kg



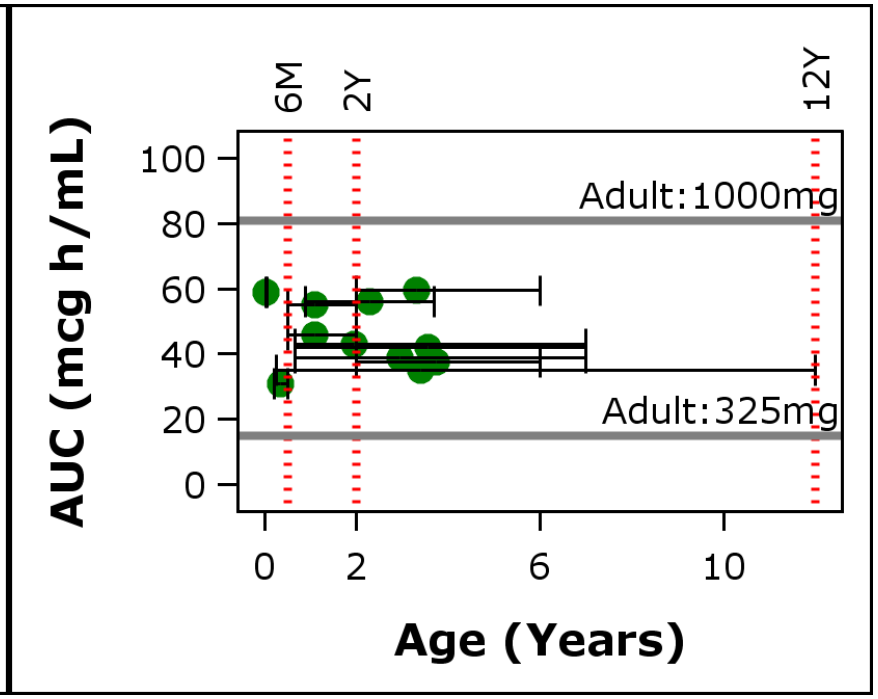
- Cmax normalized to 10 or 15 mg/kg in pediatrics is within the Cmax range in adults given currently proposed OTC monograph dose

Acetaminophen PK: AUC

Normalized to 10 mg/kg



Normalized to 15 mg/kg



- AUC normalized to 10 or 15 mg/kg in pediatrics is within the AUC range in adults given currently proposed OTC monograph dose

Summary of PK

- The exposure of acetaminophen in pediatric patients given 10-15 mg/kg orally is within the exposure range in adult subjects given currently proposed OTC monograph dose.

Outline

- Acetaminophen metabolism and the maturation of metabolic pathways
- Acetaminophen PK in pediatric patients
- Dose response relationship for acetaminophen fever reduction in pediatric patients

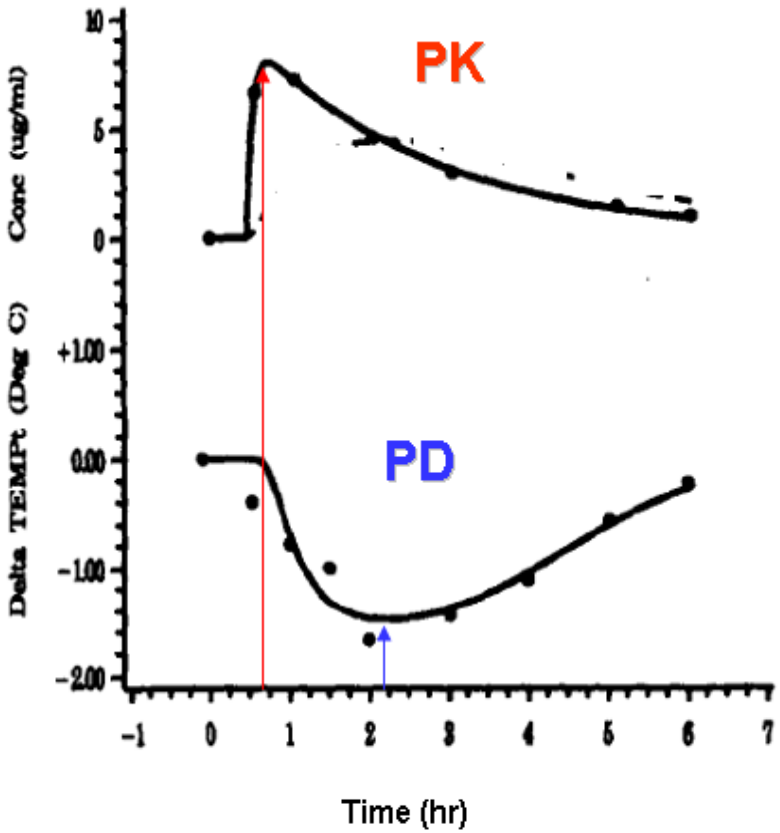
Fever Reduction: Literature Review

- Review focused on:
  - Pediatric patients less than 2 years of age
  - Oral dose
  - Single dose or multiple doses with dosing interval of every 6 hours
  - Available mean temperature versus time data up to 6 hours post dose

Fever Reduction

- Literature search Results:
  - Identified 15 pediatric fever studies
  - Age range: 2 months to 12 years
    - Studies included patients in the age range of 6 months to 2 years along with other age group pediatric patients
  - Oral dose range: 5 to 30 mg/kg
  - Fever due to variety of reasons

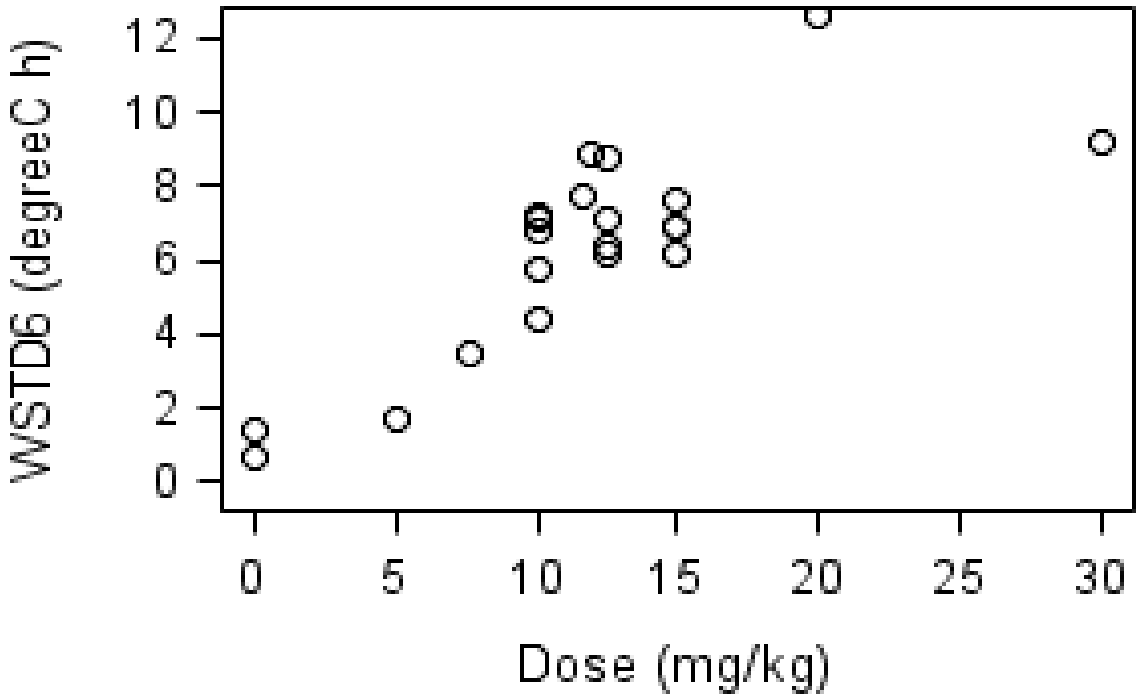
Fever Reduction: PKPD



- Delay of onset of maximum effect relative to peak plasma concentration

Brown, 1998

Fever Reduction: Dose Response



- Temperature reduction is dose dependent
- Average temperature reduction: 0.7-1.5°C for 10-15 mg/kg; <0.25 °C for placebo.

* *WSTD6: weighted sum of temperature reduction in six hours*

Summary of Fever Reduction

- A delay of the onset of maximum effect relative to peak plasma concentration was observed.
- Fever reduction is dose dependent in pediatric patients 2 months to 12 years of age.
  - Unknown number of patients in the age range of 6 months to 2 years
- Average temperature reduction: 0.7-1.5 °C for 10-15 mg/kg; <0.25 °C for placebo.

Conclusions

- Neonates and infants may be less susceptible to reactive intermediate NAPQI-associated liver toxicity.
- Exposure of acetaminophen in pediatric patients given 10-15 mg/kg orally is within the exposure range in adult subjects given the currently proposed OTC monograph dose.
- Acetaminophen dose of 10-15 mg/kg appears to be efficacious in fever reduction in pediatric patients in the age range of 2 months to 12 years.

Literature Review: Efficacy and Safety of Acetaminophen in Children 6 months to 2 years of Age

Jane Filie, M.D.
Medical Officer
Division of Nonprescription Regulation Development
Office of Drug Evaluation IV, CDER

Overview

- Antipyretic and analgesic efficacy of acetaminophen
  - Literature search
  - Summary of trials and results
  - Safety data
- Overall summary

Acetaminophen as Antipyretic

- Fever is estimated to account for one-third of all presenting conditions in children.
- Causes: infections, immunizations, inflammatory diseases, malignancies.
- Antipyretic treatment does not necessarily need to bring temperature to normal.
- Primary goal of treatment should be to improve overall comfort.

Literature Review

- Search criteria:
  - English language
  - Up to 15 mg/kg/dose
  - 6 months to 2 years of age
- Exclusion:
  - Routes of administration that not oral
  - Use of prodrug
  - Loading doses of acetaminophen

Literature Review

Fever Trials (n=51) :

- 25 were included in the review:
  - 5 placebo-controlled
  - 14 active-controlled
  - 6 comparing to physical methods of cooling
- Excluded trials:
  - Insufficient number in the target age range
  - Lacking measure of temperature change
  - Insufficient information

Literature Review

Caveat:

The 25 trials with data for age range 6 months to 2 years, also included older children:

- Many trials did not provide information on the number of children between 6 months to 2 years of age.
- Estimated relevance of the study population based on the mean age.

Fever Trials

Methodology:

- Variables not consistently controlled: room temperature, clothing, oral intake.
- Rectal vs. axillary vs. tympanic
- Inpatient vs. outpatient, or both
- Range of underlying medical conditions
- Different timing for thermometry assessments
- Different comparisons: drugs, doses

Fever Trials

Endpoints:

- Mean temperature reduction from baseline at different time points
- Mean maximal temperature reduction
- Time to temperature normalization
- Percentage of children who reached certain T or normalization
- Percentage of efficacy
- AUC over time
- Improvement of comfort

Fever Trials: Placebo-Controlled

Placebo-control +/- Active- comparator (n=5)

- Randomized, double- blind (n=2) or partial-blind (n=3), active-control trials (n=2)
- Active comparators: ibuprofen 5 and 10 mg/kg; indomethacin
- Thermometry: rectal (n=4) and axillary (n=1)
- Age range: 0-14 years across studies

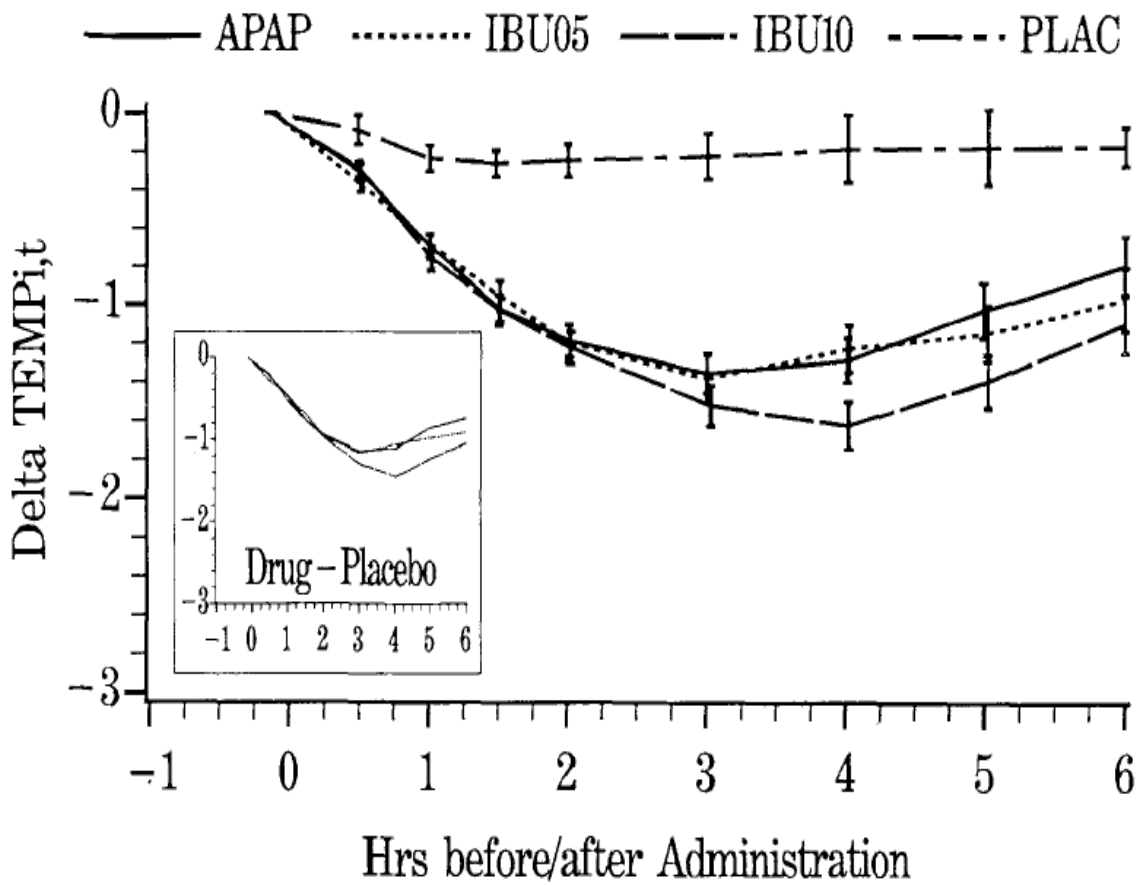
Fever Trials: Placebo-Controlled

Placebo-control +/- Active- comparator (cont.)

- All 5 studies acetaminophen superior to placebo
- Acetaminophen treatment group - at least ≥ 0.8° C temperature reduction from baseline

Fever: Placebo-Controlled

Mean changes in rectal temperature (°C) after antipyretic and placebo administration up to 6 hours after dosing (Wilson et al.)



Fever: Active-Controlled

Active-control trials (n=14)

- None demonstrated superiority of acetaminophen to active comparator
- Cannot support the antipyretic efficacy of acetaminophen from these trials

Fever: Physical Methods

Physical Methods of Cooling (n=6):

- Randomized, not double-blinded
- Non-pharmacological comparator: sponging (4), unclothing (1), combination acetaminophen + sponging (3)
- Age range: 6 w-12 y across studies
- Thermometry: rectal (n=3), axillary (n=3)

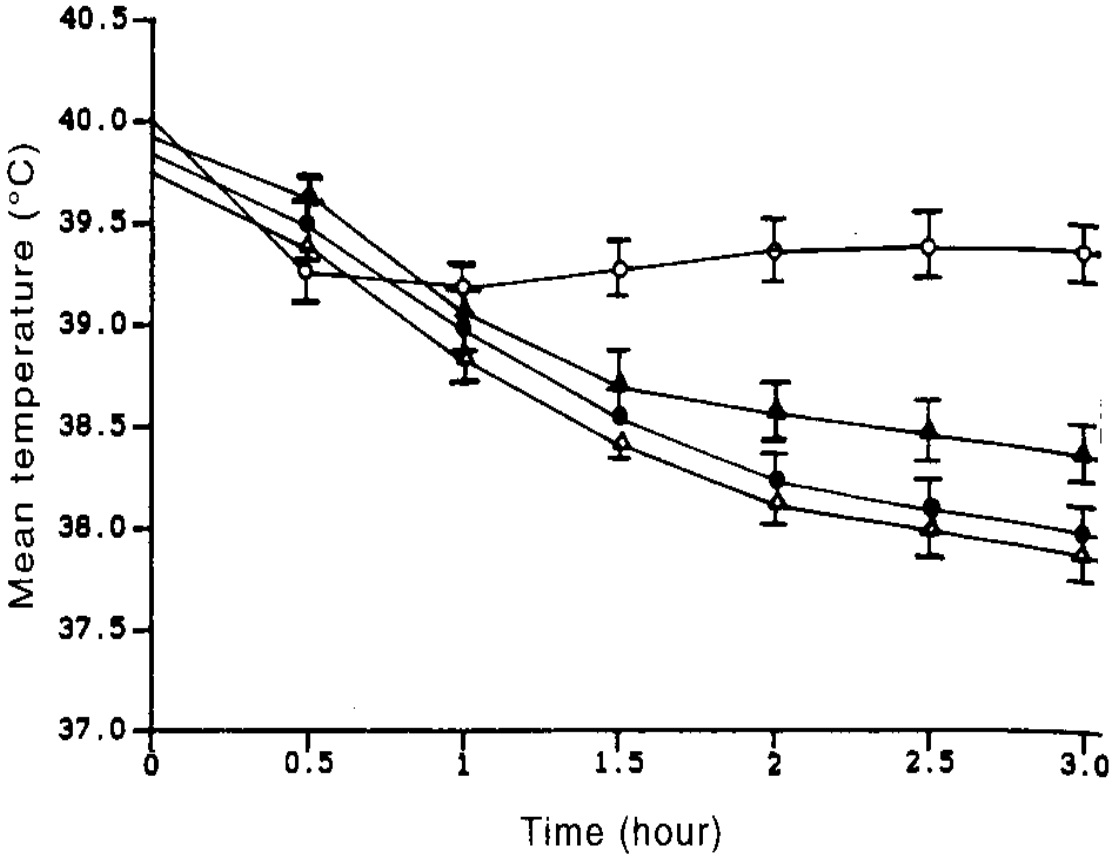
Fever: Physical Methods

Physical Methods of Cooling (cont.):

- Acetaminophen - superior to unclothing and sponging alone but not combination
- Acetaminophen - at least ≥ 1.0° C temperature reduction from baseline

Fever: Physical Methods

Mean temperatures (°C) for up to 3 hours after dosing (Aksoylar et al.)



○ -Sponging

Δ- ibuprofen 8 mg/kg

▲- acetaminophen 15 mg/kg

●- acetylsalicylic acid 8 mg/kg

Acetaminophen as Analgesic

- The OTC analgesic indication for acetaminophen is the treatment of minor aches and pains.
- The most common causes of acute pain in children in the OTC setting are:
  - illnesses: otitis media, pharyngitis
  - trauma: scrapes, soft tissue injuries, bruises sustained from normal daily activity

Literature Review

Pain Trials (n=10):

- 10 to 15 mg/kg
- 10 trials identified: 4 placebo-controlled, 5 active-controlled, 1 acetaminophen vs. no intervention
- Only acetaminophen vs. no treatment demonstrated analgesic effect

Pain Trials

- 10 Trials:
  - 1 non-surgical pain (otalgia): randomized, double-blind, placebo- and active-control
  - 9 pre-operative dosing of acetaminophen prior to myringotomy for tube placement
    - 3 randomized, placebo, placebo +/- active-control
    - 5 randomized, double-blind, active-control (no placebo)
    - 1 randomized, open-label compared to no treatment and active-control

Pain Trials: Non-surgical Pain

Otalgia study

- Randomized, double-blind, placebo- and active-control, 1-6 y.o.
- Outcome measure pain/no pain (or ear pulling) 2 days after initiation of antibiotic
- Ibuprofen superior to placebo
- Acetaminophen not statistically superior to placebo, but showed numerical difference

Pain Trials: Post-op Pain, PC

- 3 randomized, double-blind, placebo- and active-control trials
- Oral analgesic dosed 30-60 minutes prior to induction
- Ages: range 4mo to 18y, mean age approx. 2y
- Comparators: ibuprofen, ketorolac, acetaminophen + codeine
- Outcome measures: mean pain scores in PACU, need for rescue analgesia

Pain Trials: Post-op Pain, PC

- 0/3 trials demonstrated statistical superiority of acetaminophen or AC (except ketorolac)
- One trial - all patients received eardrops with lidocaine intra-operatively
  - Intraoperative medication may have masked the effect of acetaminophen
- One trial - acetaminophen vs. placebo, effect size of ~1-2 on 0-10 scale and rescue medication (acetaminophen 55% vs. placebo 76%)

Pain Trials: Post-op Pain, AC

- 5 randomized, double-/observer-blind, active-control (no placebo)
  - One abstract only (insufficient information)
- Ages: range 6mo-9y, mean age approx. 2y
- Comparators: acetaminophen + codeine, diclofenac, ketorolac, transnasal butorphenol
- Oral analgesic 20-60 minutes prior to induction
- Outcome measures: mean pain scores in PACU, need for rescue analgesia

Pain Trials: Post-op Pain, AC

- 0/5 trials demonstrated superiority of acetaminophen over comparators
- One trial:
  - all patients received fentanyl intra-operatively
  - intra-operative medication may have masked the effect of acetaminophen

Pain Trials: Comparison to No Treatment

- 1 randomized, open-label, observer-blind - abstract
- Age range: 1-5 y.o.
- 3 arms: pre-op oral acetaminophen, post op rectal acetaminophen, no treatment
- Oral analgesic given 30 minutes prior to induction, comparator post-operatively
- Outcome measure: pain scores, need for rescue

Pain Trials: Comparison to No Treatment

- Oral acetaminophen superior to rectal acetaminophen group and no treatment group for pain scores and need for rescue treatment

Overall Safety

- Adverse events: mild to moderate
- Most common: gastrointestinal (nausea, vomiting), rash, hypothermia
- Insufficient safety information following multiple dosing

Summary

Fever

- Overall - the data supportive of antipyretic effect of oral acetaminophen, 10 to 15 mg/kg

Pain

- Trials limited
  - Outcome measures coarse
  - Dosed before procedure, intra-op meds
- Limited evidence to support analgesic effect of oral acetaminophen, 10 to 15 mg/kg in patient populations studied

Review of Extrapolation: What It Is and Why We Use It

Lisa Mathis, M.D.
Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research

Definition

If scientific data supports that the course of the disease ***and*** the response to therapy are sufficiently similar in adults and children, then efficacy can be extrapolated *from adequate and well-controlled studies* in adults to the pediatric population

usually supplemented with other information obtained in pediatric patients (pharmacokinetic, safety)

Extrapolation

- Only applies to efficacy
  - Dose cannot be extrapolated
  - Safety cannot be extrapolated
  - Absorption, distribution, metabolism and elimination often differ in children based on developmental differences
  - Side effects can be different

Example of Extrapolation

- Ofirmev (acetaminophen) Injection, 10 mg/mL
- Approved 11/02/2010 for the management of mild-to-moderate pain, for the management of moderate-to-severe pain with adjunctive opioid analgesics, and for the reduction of fever in patients 2 years and older

Example of Extrapolation (con't)

- Similarity of the underlying painful conditions and the metabolic pathways that contribute to the metabolism of acetaminophen
- Efficacy extrapolated from adults
- Additional safety and pharmacokinetic data were collected in 355 patients across the full pediatric age strata, from premature neonates (≥ 32 weeks post menstrual age) to adolescents

Why Do We Use Extrapolation?

- Often, there are a limited number of pediatric patients available for enrollment in clinical trials
  - Extrapolation allows for smaller studies to support dosing and safety

Why Do We Use Extrapolation?

- Children are vulnerable and require additional safeguards because of
  - inability to communicate feelings or symptoms
  - Inability to consent

Conclusions

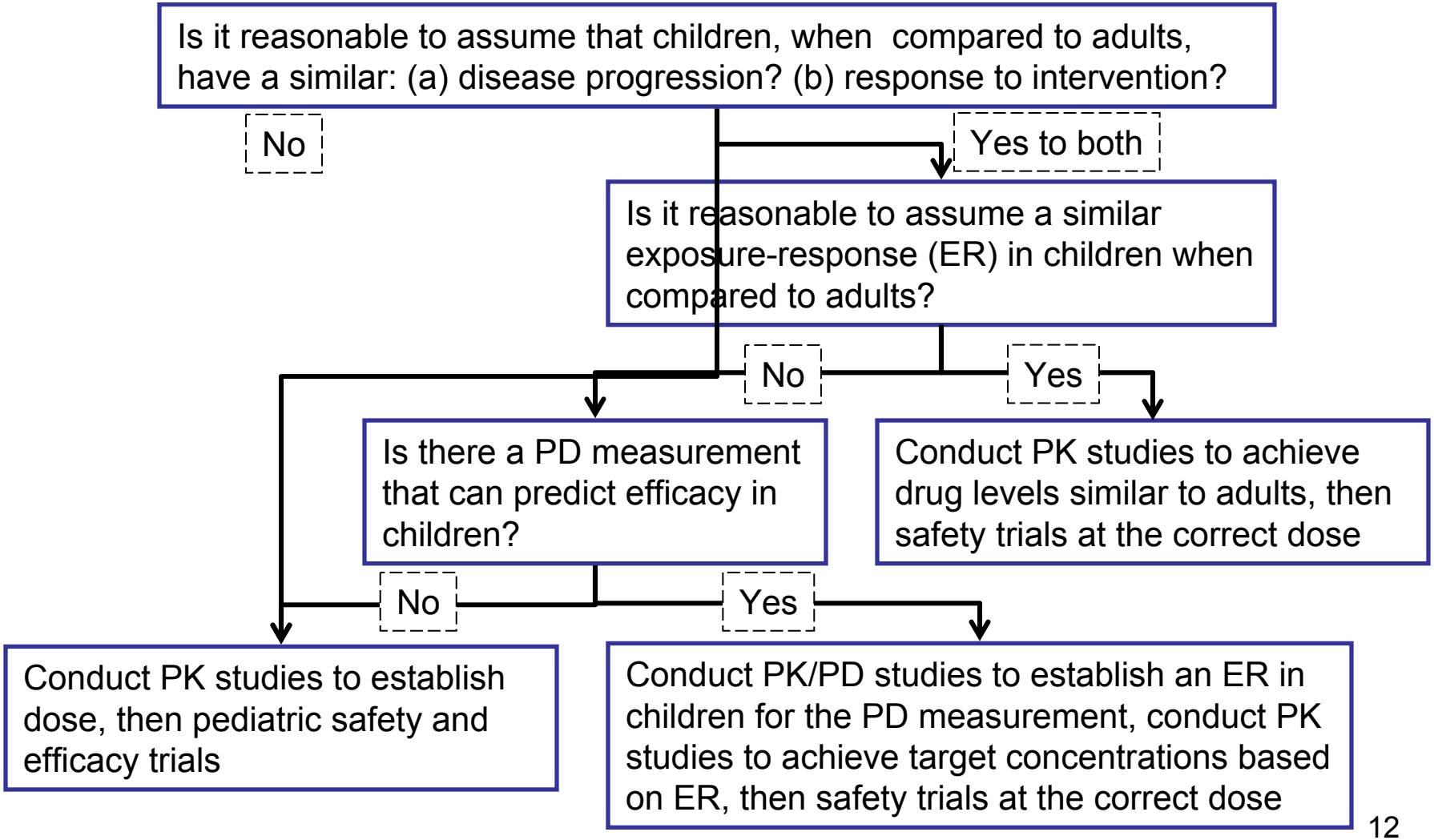
- Extrapolation is an important tool to increase the efficiency of pediatric drug development and avoid unnecessary pediatric trials
- Should be used when possible to
  - Better utilize limited resources
  - Limit exposure of children to unnecessary studies
  - Obtain trial results more quickly to increase access to efficacious medications

Backup Slides

Extrapolation Referenced in:

- 1994 Pediatric Rule
- 1999 Pediatric Rule
- 2000 International Conference on Harmonization E11
- 2003 Pediatric Research Equity Act
- 2007 FDAAA – Title IV: Pediatric Research Equity Act

Pediatric Study Decision Tree



Alternate Approach to Extrapolation

- When of the disease course or outcome of therapy in pediatric patients is expected to be similar to adults, treatment response blood levels are not clear, it may be possible to use a pharmacodynamic effect to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect.
  - A PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies

Alternate Approach to Extrapolation (con't)

– HIV Medications

- Emtricitabine, nelfinavir, ritonavir, nevirapine, lamivudine, didanosine, stavudine, abacavir, enfurvitide
- Known to lower HIV RNA, improve CD4 counts, and improve general clinical outcome in adult
- Strategy is to identify critical PK/PD relationships in adult trials then match in children
- Obtain safety data

Medication Errors Associated with Pediatric Use of Oral Acetaminophen

Irene Z. Chan, Pharm.D., BCPS
Team Leader
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)

Overview

- Background
- Adverse Event Reporting System (AERS)
- Additional Data Sources
- Points for Consideration
- Conclusions

OTC Liquid and Solid, Oral Formulations of Acetaminophen

Liquid formulation concentrations such as

- 80 mg/0.8 mL
- 80 mg/1 mL
- 160 mg/5 mL

Solid formulation strengths such as

- 80 mg (Tablet, chewable; Tablet, disintegrating)
- 160 mg (Tablet, chewable; Tablet, disintegrating)
- 325 mg (Tablet; Capsule)
- 500 mg (Tablet; Tablet, Effervescent; Capsule)
- 650 mg (Tablet; Capsule)

Medication Error Data Sources

- Adverse Event Reporting System (AERS)
  - Voluntary, “spontaneous” reports from healthcare providers and consumers reported to FDA MedWatch Program and manufacturers
- Additional Data Sources
  - Pharmacovigilance Data from McNeil
  - Poison Control Center Data

Adverse Event Reporting System (AERS)

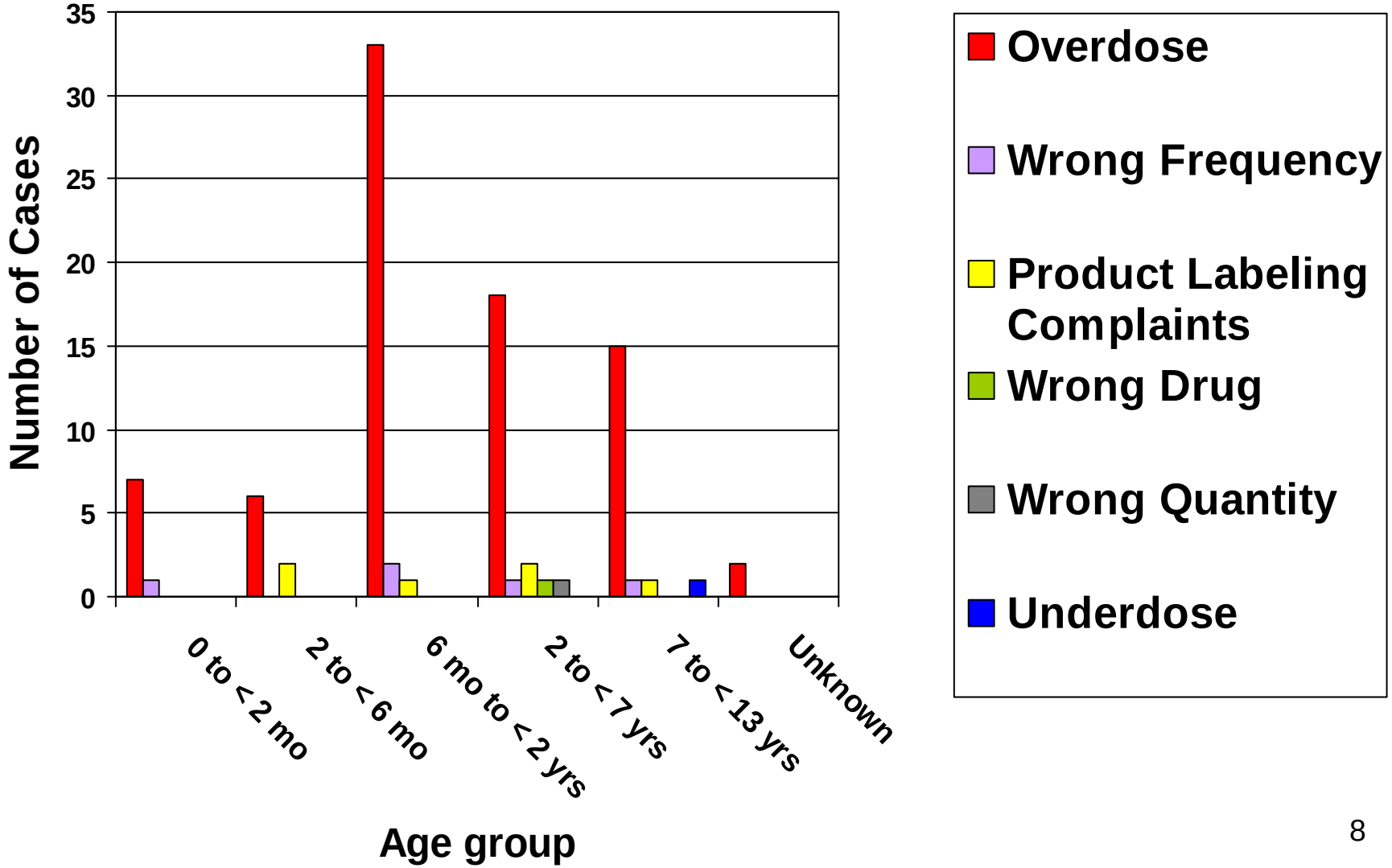
AERS Medication Error Search Criteria

- Age Limits: Age: 0 to 13 years
- Origin: Domestic
- FDA Received Date: 01/01/2000-12/31/2009
- Route of Administration: Oral
- MedDRA Terms: Medication Errors (HLGT) and Product Quality Issues (HLGT).
- Outcomes: No limitations

Categorization of Medication Errors by Type

Type of Error	# of Each Type of Error
Overdose	81
Product Labeling Complaints	6
Wrong Frequency	5
Wrong Drug	1
Wrong Quantity	1
Underdose	1

Medication Errors by Age Group



Fatal and Non-Fatal AERS Cases by Age Group

Age Group	Number of Fatal Cases (n=14)	Number of Non-Fatal Cases (n=74)
0 to < 2 months	0	8
2 mo to < 6 mo	1	5
6 mo to < 2 yrs	5	29
2 yrs to < 7 yrs	2	19
7 yrs to < 13 yrs	5	12
Unknown	1	1

* 6 of 94 cases were labeling complaints where error did not reach the patient

Serious Outcomes for Non-Fatal Cases

- Hepatobiliary (n=19)
  - elevated liver enzymes
  - hepatotoxicity (unspecified)
  - liver damage (unspecified)
- Central & Peripheral Nervous System Disorders (n=3)
  - seizures
- Renal (n=1)
  - renal failure

Fatal Cases in AERS

Fatal Case 1

- Prescriber error in 5 month old infant (weight unknown)
  - Parent instructed to administer one teaspoon (5 mL) of Infant Tylenol Drops (80 mg/0.8 mL)
  - 500 mg doses administered (unknown number of doses administered)
  - Infant developed acute liver failure

Fatal Case 2

- Adult tablet given to 9 month infant
  - Mother ran out of usual formulation
  - Adult strength acetaminophen tablet (strength unknown) crushed into formula
  - Number of doses administered was unknown
  - Infant developed acute liver failure

Fatal Case 3

- Use of Wrong Formulation in 22 month old child
  - Parent instructed to give 1 ½ teaspoons of Children's Tylenol (160 mg/5 mL) = 240 mg dose
  - Mother purchased Infant Tylenol Drops (80 mg/0.8 mL) = 750 mg dose
  - Number of doses administered was unknown
  - Infant developed acute liver failure

Fatal Case 4

- Inadequate Prescriber Instruction Regarding Formulation
  - Physician instructed mother to administer ¾ teaspoon of Tylenol to her child
  - Formulation was not specified by physician
  - Mother purchased Infant Tylenol Drops and administered 375 mg doses every 4-6 hours (number of doses administered unknown)
  - Infant developed acute liver failure

AERS Data in Previous Reviews

- Improper dose errors most common
  - Confusion between concentrated drops and other pediatric formulations

Causes of Error Identified in AERS

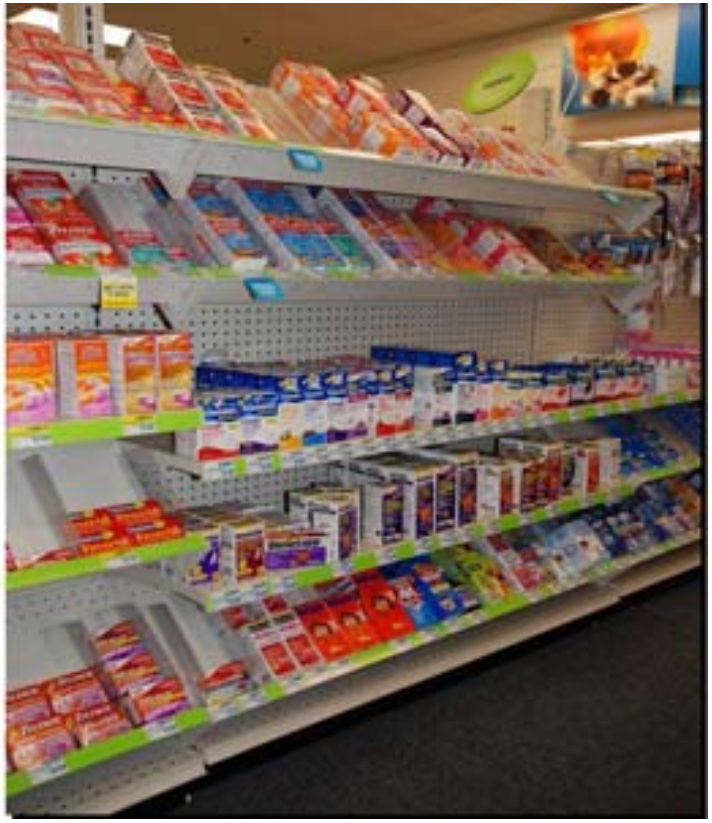
Multiple Concentrations and Formulations of Liquid Acetaminophen

Multiple Concentrations and Formulations of Liquid Acetaminophen

Therapeutic Duplication

Adult Formulation Given to Children

Prescriber Error



- Providers not specifying what formulation parents should buy or use
- Prescribing the wrong concentration

Poorly Designed Dosing Devices

Using Devices Not Co-Packaged

Labeling Complaints in AERS

- Dosing cups are not consistent across products or do not measure out the correct volume of medicine accurately
- No directions for children under 2 years of age
- Tablets not scored although directions may call for ½ tablet

Additional Medication Error Data Sources

- Poison Control Data submitted by McNeil
- Pharmacovigilance Data from McNeil

Poison Control Data

- National Capital Poison Control Center (NCPCC) in Washington, DC and the Utah Poison Control Center (UPCC) in Salt Lake City, UT
- 1,730 cases of pediatric exposures to an acetaminophen containing product, 544 of which involved errors of maladministration

Pharmacovigilance Data from McNeil

- 117 cases of drug misadministration errors received from January 1, 1992 to August 31, 2000
  - 50 cases involved Infant Tylenol Drops
  - 68 cases involved children < 2 years old
  - 50 cases had hepatic related outcomes
    - 12 resulted in death
    - 3 resulted in liver transplant

Pharmacovigilance Data from McNeil Cont'd

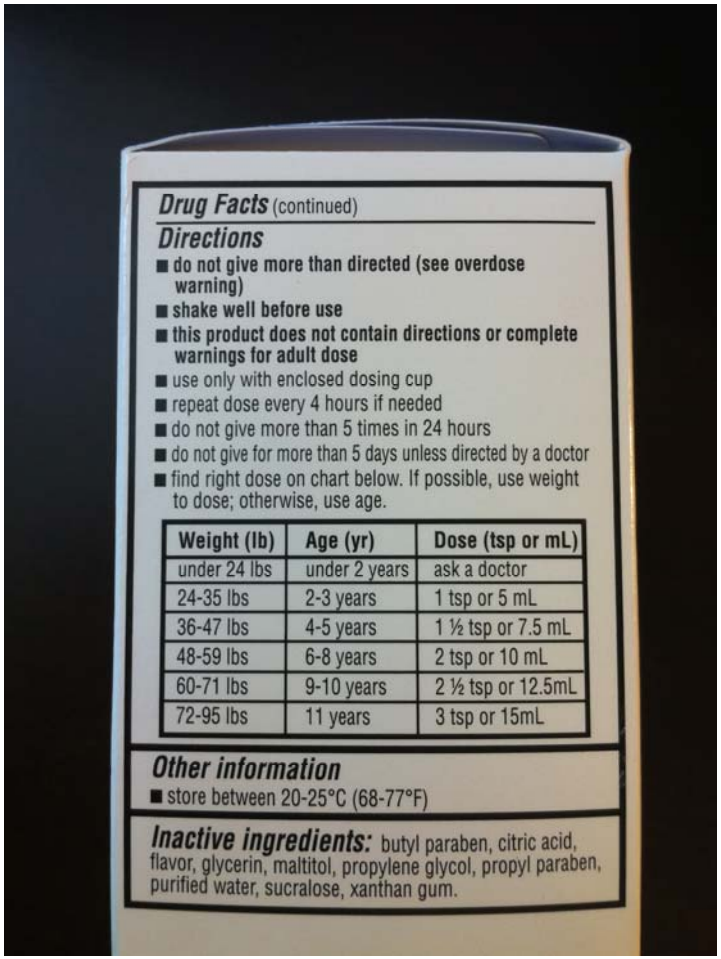
- Improper Dose Errors (overdoses)
- Wrong Time or Wrong Frequency Errors

2,209 Consumer Inquiries to McNeil

- Dosing information for children less than 2 years of age
- Dosing by age vs. dosing by weight
- Equivalency information between pediatric formulations
- Instructions on how to switch between formulations
- Confusion regarding devices included in packages (e.g. “T” for teaspoons)
- Definition of a 24 hour dosing interval

Additional Causes of Overdose Medication Errors Not Previously Identified

Dosing: Age vs. Weight



Drug Facts (continued)

Directions

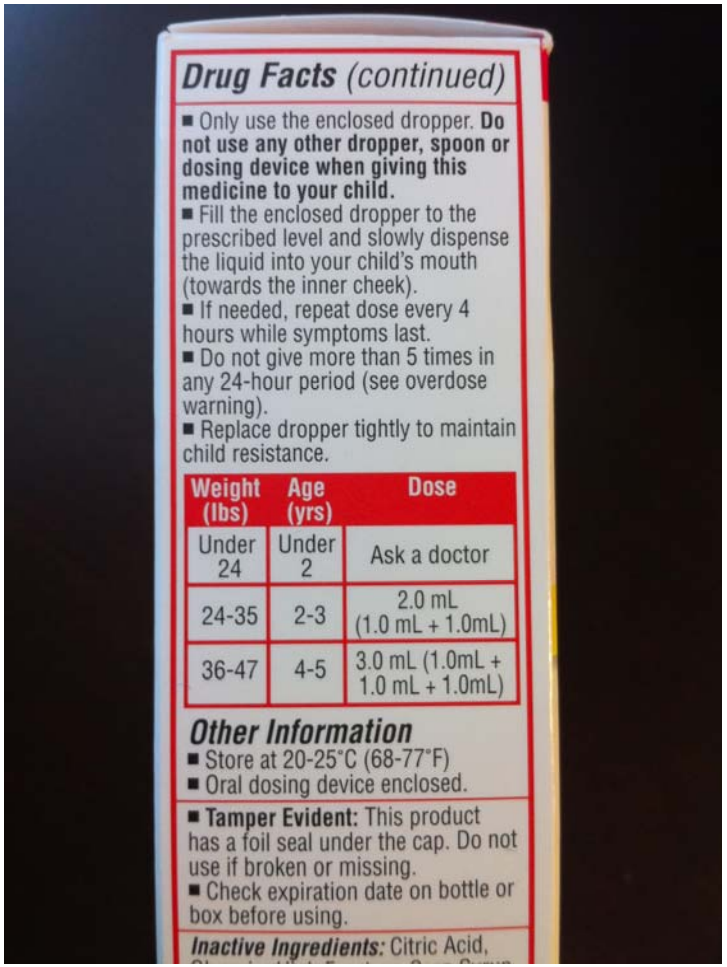
- **do not give more than directed (see overdose warning)**
- **shake well before use**
- **this product does not contain directions or complete warnings for adult dose**
- use only with enclosed dosing cup
- repeat dose every 4 hours if needed
- do not give more than 5 times in 24 hours
- do not give for more than 5 days unless directed by a doctor
- find right dose on chart below. If possible, use weight to dose; otherwise, use age.

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

Other information

- store between 20-25°C (68-77°F)

Inactive ingredients: butyl paraben, citric acid, flavor, glycerin, maltitol, propylene glycol, propyl paraben, purified water, sucralose, xanthan gum.



Drug Facts (continued)

- Only use the enclosed dropper. **Do not use any other dropper, spoon or dosing device when giving this medicine to your child.**
- Fill the enclosed dropper to the prescribed level and slowly dispense the liquid into your child's mouth (towards the inner cheek).
- If needed, repeat dose every 4 hours while symptoms last.
- Do not give more than 5 times in any 24-hour period (see overdose warning).
- Replace dropper tightly to maintain child resistance.

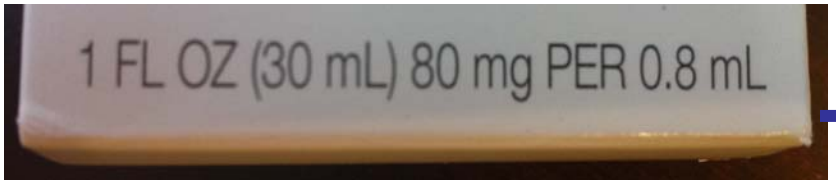
Weight (lbs)	Age (yrs)	Dose
Under 24	Under 2	Ask a doctor
24-35	2-3	2.0 mL (1.0 mL + 1.0mL)
36-47	4-5	3.0 mL (1.0mL + 1.0 mL + 1.0mL)

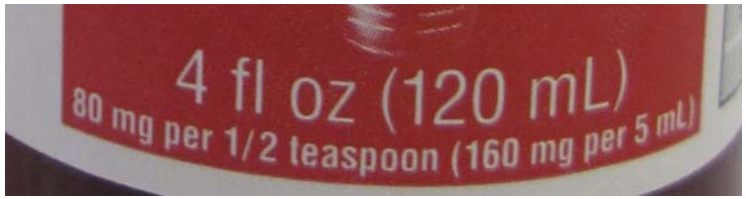
Other Information

- Store at 20-25°C (68-77°F)
- Oral dosing device enclosed.
- **Tamper Evident:** This product has a foil seal under the cap. Do not use if broken or missing.
- Check expiration date on bottle or box before using.

Inactive Ingredients: Citric Acid,

Concentrations Not Prominent





Knowledge Deficit

- Parents not aware that acetaminophen and Tylenol have the same active ingredient
- Parents unaware other products contain acetaminophen

Unit Conversion

cc

Dropperful

teaspoons

mL

Points for Consideration and Conclusions

Amendment of TFM

- Amending the tentative final monograph (TFM) for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products to limit to OTC marketing of a single concentration for liquid, pediatric formulations of acetaminophen will allow enforcement

Education is Needed

- Caregivers & Healthcare Providers
  - Varying formulations
  - Varying concentrations
  - Presence of acetaminophen in multiple products with different family trade names
  - Implications of therapeutic duplication
  - What formulations are appropriate for children
- Healthcare Providers
  - Recognize signs and symptoms of acetaminophen toxicity
  - How to properly treat acetaminophen toxicity

Add Pediatric Dosing

- Add dosing information for children down to at least 6 months of age in the Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) TFM

Device Considerations

- Standardized dosing device needed
- Monograph regulations do not provide for inclusion of specific dosing devices or review of devices prior to marketing

Device Considerations Cont'd

- Integrate a measuring device with the product container closure if feasible
- Should have easily visible measurement markings.
- Should not be able to administer more medication than would be needed for usual dosage

Device Considerations Cont'd

- Remove confusing and non-metric abbreviations and ensure that milliliter designations are provided on measuring devices using the standardized abbreviation 'mL'
- When abbreviations are utilized, ensure that they are defined and consistent with directions on labeling
- Usability testing needed

Directions on Labeling

- Single, standardized chart expressing doses with the same units of measure across manufacturers
  - Must coordinate with dosing device development
  - Chart must be validated through label comprehension studies before being introduced to the market

Accidental Ingestions

- 120 cases identified in AERS database
- Causes
  - Misadministration by young siblings (e.g. 3 year old gives 1 year old sibling medicine from an open bottle)
  - Medication tastes sweet or like candy
  - Caps removed by children
    - Unknown if these were child resistant caps

Measures to Help Prevent Accidental Ingestions

- Ensure child-resistant closures
- Barriers in package designs to prohibit easy emptying of contents

Conclusions

- Most common type of medication error across all age groups is overdose
- More than half of medication errors reported in AERS were in children < 2 years of age
- Medication errors have led to serious outcomes including death
- Overdose medication errors can be prevented, but change in regulations is required

Single-Ingredient Acetaminophen Utilization Patterns

Tracy Pham, Pharm.D
Drug Use Analyst
Division of Epidemiology II
May 17-18, 2011

Outline

- National over-the-counter (OTC) sales data
- Outpatient retail prescription (Rx) data
- Limitations
- Summary

Over-the-Counter Sales Data
Years 2001-2009

IMS Health, IMS National Sales Perspective™

Database Description
IMS Health, IMS National Sales Perspective™

- Measures the volume of prescription (Rx) and OTC drug products sold from manufacturers to retail and non-retail channels of distribution
- **Eaches (EA)** are the number of packets, bottles, or vials of a product shipped in a unit
- Retail settings include: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service
- Non-retail settings include: clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings

Overall Sales Market of OTC and Prescription Acetaminophen Products, Y2001-2009

IMS Health, IMS National Sales Perspective™. Years 2001-2009. Extracted September and December 2010.

- Sale of OTC and Rx acetaminophen products increased by ~38% between y2001 and y2009
- Y2009: ~438 million bottles/packets were sold
  - OTC: 81% of total market (356 million)
    - Combination: 58% of OTC market
    - Single-Ingredient: 42% of OTC market
  - Rx (combination): 19% of total market

Over-the-Counter Single-Ingredient Acetaminophen Products

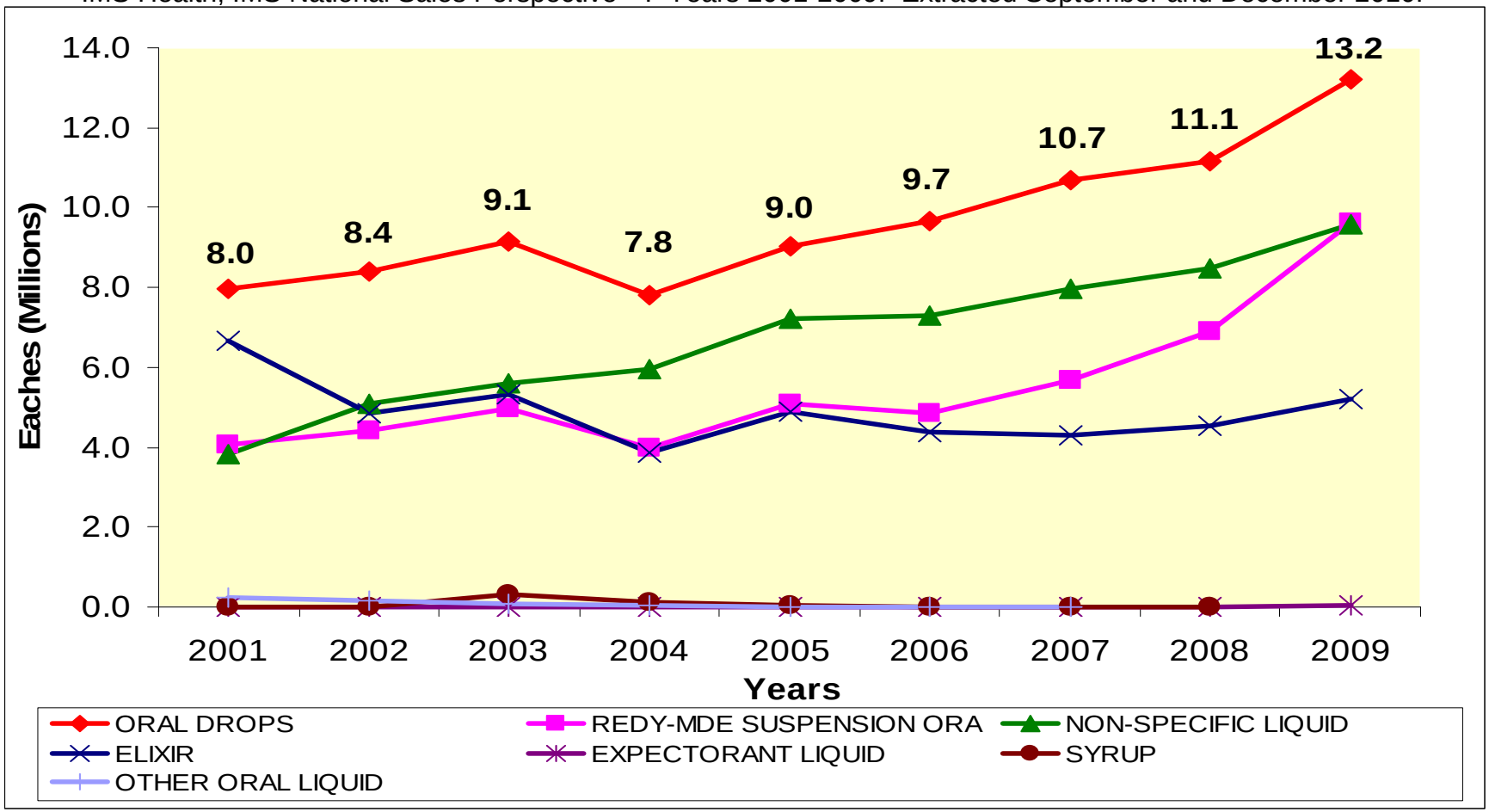
Sales of OTC Single-Ingredient Acetaminophen Products, Y2001-2009

IMS Health, IMS National Sales Perspective™. Years 2001-2009. Extracted September and December 2010.

- ~35% increase in sales between y2001 & y2009
- Y2009: ~151 million bottles/packets were sold
  - Oral solid formulations: ~65% of sales (98.6 million)
  - Oral liquid formulations: ~25% of sales (37.6 million)
    - Concentrated oral drops accounted for ~35% of sales of oral liquid formulations (13.2 million)
  - Oral solid long-acting formulations: ~9% of sales
  - Rectal formulations: <1% of sales

Sale of Oral Liquid Formulations of OTC Single-Ingredient Acetaminophen Products, Y2001-2009

IMS Health, IMS National Sales Perspective™. Years 2001-2009. Extracted September and December 2010.



Sales of OTC Single-Ingredient Acetaminophen by Product Strength, Y2009

IMS Health, IMS National Sales Perspective™. Year 2009. Extracted October 2010.

OTC Single-Ingredient	%
500mg	*47.1*
160mg	*15.9*
325mg	*13.8*
80mg	*11.7*
>500mg	*9.6*
120mg	*0.3*
300mg	*0.2*
All Others	*1.5*

Prescription-Level Data

Years 2000-2009

SDI, Vector One®: National (VONA)

Database Description
SDI, Vector One®: National (VONA)

- National-level projected prescription and patient-centric tracking service
  - Over 1.4 billion prescription claims per year
  - Over 120 million unique patients
  - Approximately 59,000 U.S. retail pharmacies

- Retail pharmacies include:
  - National retail chains
  - Mass merchandisers
  - Pharmacy benefits managers and their data systems
  - Provider groups

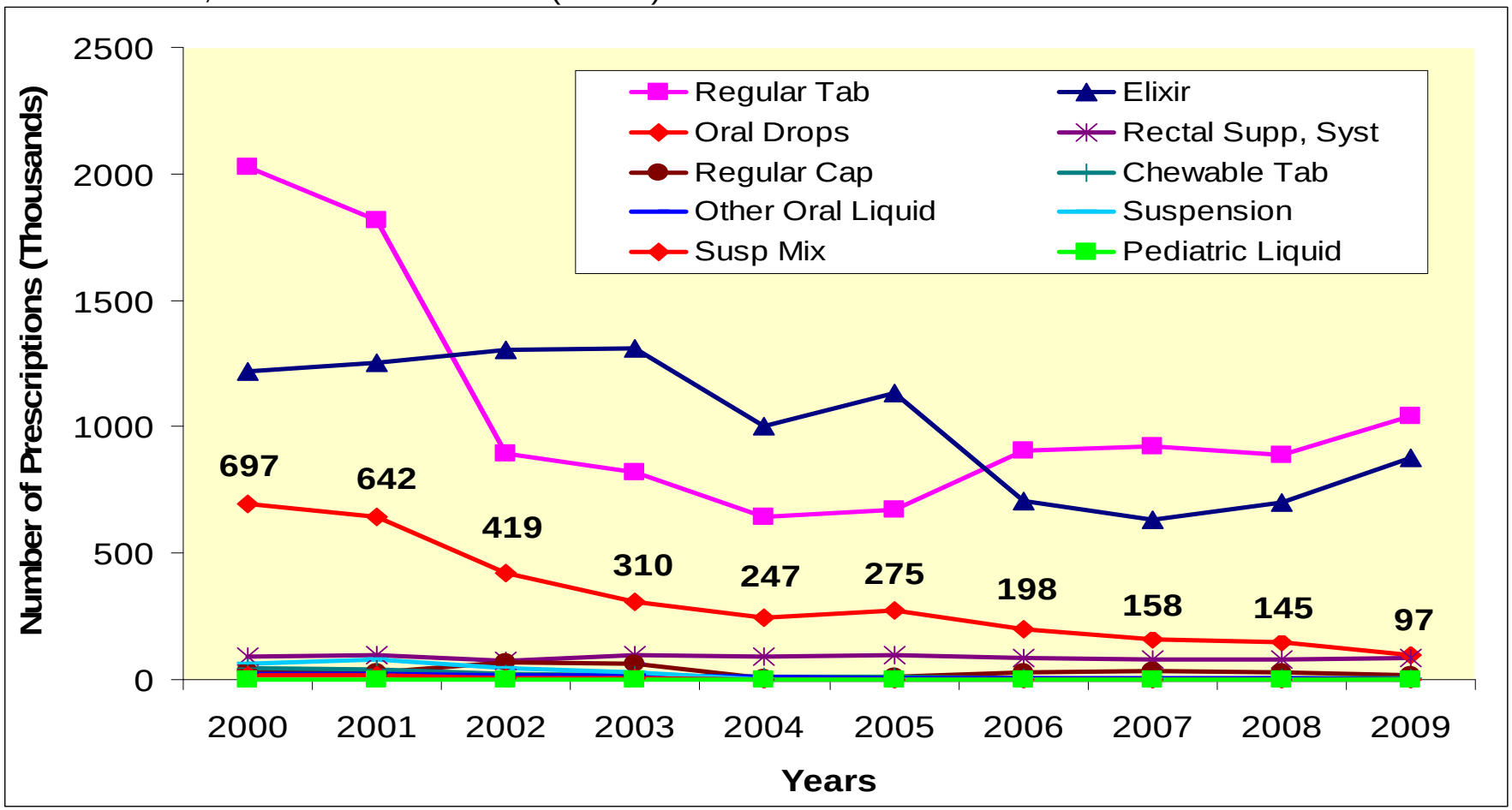
Projected Number of Dispensed Prescriptions for Single-Ingredient Acetaminophen Products, Years 2000-2009

SDI, Vector One®: National (VONA). Years 2000-2009. Extracted December 2010.

- ~50% decrease in number of dispensed prescriptions
- Y2009: ~2.1 million prescriptions dispensed
  - Concentrated oral drops: ~5% of single-ingredient acetaminophen (97,000 prescriptions)

Projected Number of Dispensed Prescriptions for Single-Ingredient Acetaminophen Products by Dosage Form, Y2000-Y2009

SDI, Vector One®: National (VONA). Years 2000-2009. Extracted December 2010.



Percentage of Single-Ingredient Acetaminophen Dispensed by Product Strength, Y2009

SDI, Vector One®: National (VONA). Year 2009. Extracted December 2010.

Rx Single-Ingredient	%
160mg	*41.3*
500mg	*34.1*
325mg	*16.2*
80mg	*3.0*
120mg	*2.3*
650mg	*1.2*
300mg	*0.0*
All Others	*1.9*

Limitations

- OTC sales analysis
  - Sales from manufacturers to various channels of distribution
  - Captured approximately 50% of all OTC sales
  - Using sales volume as surrogate for use
    - Unable to determine user numbers or demographics
    - Unable to determine frequency or amount of OTC products purchased or used at the consumer level
    - Unable to determine concurrent product use
- Dispensed prescription analysis
  - Only describing outpatient prescription use
    - Products captured only as a prescription claim
    - OTC sales not captured

Summary

- Sales of OTC single-ingredient acetaminophen products increased by ~35% with 151 million bottles/packets sold in y2009.
- Concentrated oral drops formulation was the most commonly sold oral liquid formulation for OTC single-ingredient acetaminophen products.
- Sale of OTC concentrated oral drops formulation increased by 66% from y2001 to y2009.
- OTC strengths (80mg, 120mg, and 160mg) most likely to be used in pediatrics accounted for almost a third of total sales.

Acetaminophen-Exposure Associated Problems in Children in the U.S:

A review of U.S. poison control center calls data for 2002-8

May 17-18, 2011 Advisory Committee Meeting

Margie R. Goulding, Ph.D.

Study Objectives

- Measure magnitude of problem associated with over/exposure to acetaminophen in children (particularly <2 year olds) in the U.S.

  1– broadly, in acetaminophen-only exposure calls to poison centers

  2– only overdose calls/cases

  3– cases w/ outcomes associated w/ acetaminophen-only over/exposures, e.g. hepatic related abnormality, severe medical outcomes & health care facility use

- Evaluate changes in these measures over 2002-2008

Data Source Description

- **National Poison Data System (NPDS)**
  - National database -- poison centers (PCs) contribute data from calls they receive (2008):
    - 2.49 mln closed human exposure cases
    - 1.7 mln information calls
- All 61 PCs participated in NPDS in 2008.
- PCs serve entire U.S. population.
- Calls routed through 1-800-222-1222
- Anyone in U.S. with access to a phone has access to a PC (free) 24/7 all year.
- PCs are managed & staffed by health care professionals w/ toxicology training

Analytic Approach

- **Descriptive analysis of calls data (counts) by various measures:** call reason, overdose, & outcomes:
  - Clinical: hepatic related abnormality, severe medical outcomes, and
  - Health care use: health facility use, overdose treatment with activated charcoal or N Acetyl Cysteine (NAC)
- **Examination of population-based rates of these measures** (calls per 1 mln pop.)
  - Differences across age subgroups
  - Changes over time

Definitions

"Overdose" -- any of these 3:

1. Report of a ten-fold dosing error (n=220)
2. Exposure at level 5 times > Kaiser's recommended dosing levels for children
3. Exposure > AAPCC's guidelines for referral to emergency dept.:
   - For patients <6 years of age:
     - ≥200 mg/kg over 8–24 hours
     - ≥150 mg/kg/day for 2 days
     - ≥100 mg/kg/day for 3 days or longer
   - For for patients ≥6 years of age:
     - ≥10 g or 200 mg/kg (whichever is less) over a single 24-hour period
     - ≥6 g or 150 mg/kg (whichever is less) per 24-hour period for 48+hrs

"**Severe Medical Outcomes":** *death, major (life-threatening/ disabling) effect* or *moderate effect*

Definitions

- Hepatic Related Abnormality: indicated by any of these 5:
  - (i) 100< AST, ALT <=1,000
  - (ii) AST, ALT >1,000
  - (iii) PT (Prothrombin Time) prolonged
  - (iv) Other coagulopathy
  - (v) Other LFT (Liver Function Test) abnormality
- Health Care Facility Use
- Charcoal/NAC Therapy Recommended or Administered

AST: aspartate aminotransferase, ALT: alanine aminotransferase, NAC: N-acetyl cysteine

Results: Case Reason

SINGLE Substance Acetaminophen-ALONE EXPOSURE Calls in Children (<18 yrs old), total for period 2002-08: **265,558 calls** **(~ 25% in <2 yr olds)**

Breakdown by REASON of these 265,558 calls:

Categories w/ LARGE counts:

- **Unintentional--General** (proxy for unsupervised child ingestions): **171,730 calls (64.7%)**
- **Unintentional--Therapeutic Error: 62,420 (23.5%)**
- **Intentional–Suspected Suicidal: 23,372 (8.8%)**

Categories w/ Medium-Small counts:

- Intentional--Misuse/Abuse: 3,440 (1.3%)
- **Adverse Drug Reactions: 845 (0.32%)**

2 Case Groups Created:

"Unsupervised Kids" (n=187,066):

- Unint-General cases in kids<6 yrs old:
- Int-Suicidal/Abuse/Misuse, kids 11-17 yrs old

"Therapeutic Mishaps" (n=63,265):

- Therapeutic error cases, ages 0-17 yrs
  - -- ~53% in <2 year olds
- Adverse Drug Reaction cases, ages 0-17 yrs

Results – Static Measures of Acetaminophen-Exposure Associated Problems in Children (case counts, for 2002-2008 period)

Outcome Measure	Group 1: All Single Substance Acetaminophen Alone Exposure cases (0-17 yr olds) **265,558**	Group 2: "Unsupervised Kids" cases **187,066**	Group 3: **"Therapeutic Mishaps" cases** **63,265**
OVERDOSE	31,328 (11.8%)	**24,790 (13.3%)**	3,876 (6.1%)
< 2 yrs	1.9%	2.8%	0.8%
2-6 yrs	12.9%	13.6%	7.5%
7-12 yrs	18.7%	18.9%	18.3%
13-17 yrs	26.3%	29.0%	18.1%

Data Source: NPDS

Results – Static Measures of Acetaminophen-Exposure Associated Problems in Children (cases, 2002-2008)

Clinical Outcomes	Group 1: All Single Subst Acet Alone Exp cases (0-17 yr olds) **265,558**	Group 2: "Unsupervised Kids" cases **187,066**	Group 3: "Therapeutic Mishaps" cases **63,265**
Hepatic Related Abnormality	2381 (0.90%)	1992 (1.06%)	148 (0.23%)
Severe Medical Outcome	3986 (1.50%)	3352 (1.79%)	210 (0.33%)
Deaths	17 (0.01%)	6 (<0.01%)	7 (0.01%)

Data source: NPDS

Results – Static Measures of Acetaminophen-Exposure Associated Problems in Children (cases, 2002-2008)

Health Care Resource Use Outcomes	Group 1: All Single Subst Acet Alone Exp cases (0-17 yr olds) **265,558**	Group 2: "Unsupervised Kids" cases **187,066**	Group 3: "Therapeutic Mishaps" cases **63,265**
Health Care Facility Use	56,880 (21.4%)	50,935 **(27.23%)**	2,327 (3.68%)
Charcoal/NAC Therapy Recommended /Performed	33,045 (12.44%)	30,527 **(16.32%)**	474 (0.75%)

Data source: NPDS

Results – (full case set*)
Changes in **Pop-Based Rates** Over 2002-8

Outcome Measure --age group	Year 2002 Rate (per 1 mln pop.)	Year 2008 rate (per 1 mln pop.)	Change: % direction
Overdose			
-- 0-17 yr olds	55	71	29% increase
-- <2 yr olds	19	30	**60% increase**

Data Source: NPDS

*Full case set = all single substance exposure calls for acetaminophen alone in children (<18 yrs old), years 2002-8 (n=265,558), which includes large number of unsupervised child ingestions

Results for **Therapeutic Mishaps** Cases: Changes in Pop.-Based rates over 2002-8

- **Overdose rates:**
  - Increased 27% in 0-17 yr olds from 438 to 616 per mln
  - Increased 37% in <2 yr olds from 1071 to 1558 per mln

Other outcomes, ALL low Rates, But All INCREASED:

- **HRA** Rates: <0.5 per mln & went **up 25%** in 0-17 yr olds,
  <2 per mln & went **up 9%** in <2 yr olds

- **SMO** rates: <0.6 per mln & went **up 24%** in 0-17 yr olds,
  <2 per mln & went **up 17%** in <2 yr olds

- **HCF Use** rates: <6 per mln & went **up 36%** in 0-17 yr olds,
  <25 per mln & went **up 45%** in <2 yr olds

HRA=Hepatic Related Abnormality, SMO=Severe Medical Outcomes, HCF=Health Care Facility

Source: NPDS

Other Interesting Results

- **Overdose correlates with clinical effects & health care facility use but not with deaths** – due to intervention (& under capture?)
- Calls for Acetaminophen Therapeutic Errors in kids (0-17 yrs old) over 2002-8 period (N=62,420)

Top 4 Therapeutic Errors:

1. giving/taking medication twice (N=21,312) or **34.1%**
2. giving/taking doses too close together (N=7123) or **11.4%**
3. giving incorrect formulation/concentration (N= 5645) or **9.0%**
4. dispensing cup/device errors (N= 3062) or **4.9%**

Source: NPDS

Limitations

- Voluntary calls ➔ underascertainment
  - Low # of deaths (under capture?)
- Callers motivated to call PCC for medical advice, unless:
  - Intent on suicide?
  - Already rushing to ED?
- No information on full number of persons exposed to acetaminophen
- Majority of calls had inexact dosage
- No statistical trend tests done on the call rates

Key Findings

- **Acetaminophen exposure in kids still generating problems:**
  - 32,000 - 46,000 PCC calls/year (~25% in <2 year olds)
  - Majority for unsupervised ingestions in <6 year olds or intentional suicide/ abuse/ misuse by teenagers
- **Acetaminophen over/exposure problems in kids, on most measures, in most of the age subgroups, including the <2 year olds, appear to have increased over 2002-2008 period.**
- **Acetaminophen therapeutic error calls in kids were**
  - **~ 9,000/year over 2002-8 period**
  - ~ 53% in <2 year olds
  - 45% of the errors from giving medication twice or doses too close together

Hospitalization Rates for Acetaminophen-associated Poisonings in Children

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Outline

- Objective
- Background
- Methods
- Results
- Limitations
- Key Findings
- Acknowledgements

Objective

To estimate rate of hospitalizations due to acetaminophen-associated poisonings in children.

Background

- The Nationwide Inpatient Sample (NIS) is the largest national all-payer hospital inpatient care database in the US
  - Nearly 8 million hospital stays/year from 1,000 hospitals
  - Provides national estimates
- The sampling frame for NIS data comprises 95% of all U.S. discharges

Methods

- Data analyzed from 1998-2008
- The unit of analysis is hospital discharge (not patient)
- Acetaminophen-associated poisoning identified through any discharge diagnosis for ICD-9-CM codes:

  --965.4: Poisoning by aromatic analgesics (AA) not elsewhere classified (NEC)

  --E850.4: Accidental poisoning by AA NEC

Methods---(2)

- Hepatotoxicity (if coded in addition to Acetaminophen-associated poisoning code)
  - DX 572.4 (hepatorenal syndrome)
  - DX 572.2 (hepatic coma/hepatic encephalopathy)
  - DX 570 (acute or subacute liver necrosis/acute hepatic failure)
  - DX V42.7 (liver transplant)
  - PR 50.5 (any encounter that listed liver transplant as a procedure code)
  - DX 782.4 (jaundice)
  - DX 286.9 (coagulopathy)
  - DX 286.7(coagulation defect due to liver disease)
  - DX 791.4 (biliuria)
  - 790.4 (transaminsasemia)
  - 573.3 (hepatitis, noninfectious toxic)

Methods---(3)

- Rates per 100,000 U.S. population were estimated
  - Numerator – number of projected hospital discharges
  - Denominator – U.S. population in specified age groups, as reported in the U.S. census 1998-2008, in July of each year
- Data were analyzed using SAS and SUDAAN
- Trend analyses
  - Statistical significance across time was evaluated by comparing the 95% confidence interval around the estimate in period 1 (1998-1999) to that for period 4 (2006-2008)

Results

Rates of Acetaminophen-associated Poisoning Discharges per 100,000 U.S. Population, by Age

	1998-1999	2000-2002	2003-2005	2006-2008
	Rate	Rate	Rate	Rate
	(95% CI)	(95% CI)	(95% CI)	(95% CI)
All Acetaminophen poisoning				
All ages	10.96 (10.92 -11.01)	11.70 (11.66 -11.73)	12.29 (12.25 -12.33)	14.86 (14.82 -14.90)
< 2 years	**2.07 (1.96 -2.19)**	**1.38 (1.31 -1.46)**	**1.95 (1.86 -2.04)**	**1.69 (1.61 -1.77)**
2-12 years	**1.19 (1.15 -1.22)**	**1.60 (1.56 -1.63)**	**1.61 (1.57 -1.64)**	**1.35 (1.32 -1.38)**
13-17 years	33.59 (33.30 -33.88)	32.50 (32.27 -32.73)	28.88 (28.67 -29.09)	26.04 (25.84 -26.25)
18+ years	11.20 (11.15 -11.25)	12.20 (12.16 -12.24)	13.23 (13.19 -13.27)	16.95 (16.90 -17.00)

Data Source: NIS 1998-2008

Rates of Acetaminophen-associated Poisoning Discharges with Hepatotoxicity, per 100,000 U.S. Population, by Age

	1998-1999	2000-2002	2003-2005	2006-2008
	Rate	Rate	Rate	Rate
	(95% CI)	(95% CI)	(95% CI)	(95% CI)
All Acetaminophen poisoning				
All ages	1.330 (1.314 -1.345)	1.663 (1.649 -1.677)	1.901 (1.886 -1.916)	2.370 (2.354 -2.387)
< 2 years old	**0.300 (0.256 -0.345)**	**0.103 (0.082 -0.124)**	**0.145 (0.120 -0.169)**	**0.146 (0.122 -0.170)**
2-12 years	**0.040 (0.033 -0.046)**	**0.085 (0.077 -0.093)**	**0.098 (0.089 -0.107)**	**0.037 (0.032 -0.042)**
13-17 years	1.658 (1.594 -1.723)	2.154 (2.094 -2.213)	1.689 (1.637 -1.741)	1.618 (1.567 -1.668)
18+ years	1.613 (1.594 -1.633)	2.005 (1.987 -2.022)	2.350 (2.331 -2.369)	2.981 (2.960 -3.002)

Data Source: NIS 1998-2008

Inpatient Mortality in Children with Acetaminophen-associated Poisonings

- Overall, 63 deaths found in the child hospitalizations with a diagnosis code of acetaminophen-poisoning in the 1998-2008 period (but these cases could also have had other codes as well)
- Overall there were 76,810 hospitalizations in children less than 18 years of age in this 11 year period

Limitations

- Unit of analysis is hospital discharge (not patient); patients with multiple hospitalizations could be counted multiple times
- Underestimation of total discharges
  - Excludes poisonings treated in federal hospitals and outpatient settings
- Medical records are not available to validate diagnoses
- Data are based on administrative records that are used for billing purposes and clinical details are limited
- Poisonings from other drugs and other relevant medical conditions were not excluded
- Not able to determine circumstances surrounding poisoning
  - Unable to distinguish unsupervised ingestion vs. therapeutic errors

Key Findings

- Rate of hospitalizations across all ages increased from 10.96 per 100,000 pop. in 1998-99 to 14.86 per 100,000 pop. in 2006-08
- Overall rate of hospitalizations <u>has declined</u> among < 2 year olds
- Rate of hospitalizations with hepatotoxicity across all ages increased from 1.33 per 100,000 in 1998-99 to 2.37 in 2006-08
  - No significant change for 13-17 year olds or 2-12 year olds
  - 50% decline in hospitalizations for children <2 from 0.300/100,000 in 1998-99 to 0.146/100,000 in 2006-08

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Review of Acetaminophen Post marketing Adverse Event Reports and Medical Literature

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Overview

- Background
- Adverse Event Reports
- Literature
- Conclusions

Background

- 23% of surveyed households give at least 1 dose of acetaminophen to their 0-23 month old children each week.[1]
- 70% of all acetaminophen adverse events are unintentional overdose.[2]
- 2/3 of unintentional overdose events are among children < 12 years old.[2]

FDA Adverse Event Reporting System (AERS)

- Voluntarily reported adverse events (however, companies have variable reporting requirements)
- Passive surveillance system
- Human drug and therapeutic biologics
- Useful for identifying events with rare background rate.

AERS Limitations

- Underreporting
- Variable quality
- Reporting biases
- Difficult to attribute events with high background rates or long latency periods to the product
- Not useful for true incidence rates; problematic for comparing drugs in the same class.

OSE AERS Search

- All serious* domestic adverse event reports associated with single ingredient acetaminophen products without concomitant medications
- Children 0 to 2 years of age
- Received by FDA from January 1, 2000 through December 31, 2009
- Total number of cases n = 92
  - 89 Non-Fatal cases
  - 3 Fatal cases

* 21 CFR 314.80

AERS Deaths

- 3 deaths age < 2 years
- Ages: 1, 18, 22 months
- Deaths due to unintentional overdose
- Cause: Hepatic failure
- Incomplete data; but consistent with > 1 day of supra-therapeutic doses

Serious Non-Fatal AERS Cases

Primary Adverse Event Category	Cases for < 2 Years Old (n)
Gastrointestinal	30
Allergic reaction / Rash	21
Irritability	8
Sleep disturbances	8
Convulsion / Seizure	5
No drug effect	4
Renal	3
Respiratory	3
Bleeding	2
Hepatic	2

Table displays primary adverse event categories with ≥ 2 cases reported

Medical Literature Review

Hepatic Events: Sources of Data

- NPDS (2005-2009)[3]
  - Children 0-5 years old
  - 337 to 400 received N-acetylcysteine per year
- AERS (2000-2009)
  - Children 0-5 years old
  - Total: 2 serious non-fatal hepatic cases

Acetaminophen Dose for Children

- Systematic analysis of 32,414 pt in Clin Trials[4]
- Dose: > 98% ≤ 60 mg/kg/day
- Key conclusion: hepatotoxicity rarely reported with therapeutic dosing in defined population
- Limits:
  - Excluded subjects
  - Assay sensitivity

AAPCC Recommendation for Emergency Department Referral by Acetaminophen Duration and Dose[5]

Hours of use	Average dose mg/kg/day
24	200
48	150
72	100

OSE Conclusions

- No new or unexpected safety signals from AERS identified with pediatric acetaminophen use.
- NPDS data show many more cases of severe hepatic toxicity than AERS.
- Overall, data are insufficient to provide a dose recommendation.

References

1. Vernacchio L, Judith P. Kelly JP, Kaufman DW, et al. Pediatrics 124:446;2009
2. Willy M, Kelly JP, Nourjah P, et al. Pharmacoepi Drug Safety 18:188; 2009
3. Bronstein AC et al. Clin Tox 2007-2010
   Lai MW et al. Clin Tox 2006
4 Lavonas EJ, Reynolds KM, Dart RC Pediatrics 126:e1430;2010
5. Dart RC.,Erdman AR, Olson KR, et al. Clinical Toxicology 44:1; 2006