BRIEFING MATERIALS

FOR

DRUG SAFETY AND RISK MANAGEMENT
ANESTHETIC AND LIFE SUPPORT
AND NONPRESCRIPTION DRUGS
ADVISORY COMMITTEE MEETING
JUNE 29-30, 2009

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SECTION 1 EXECUTIVE SUMMARY

EXECUTIVE SUMMARY

McNeil Consumer Healthcare Division of Mc-Neil-PPC, Inc. (McNeil) is a major manufacturer of over-the-counter (OTC) drug products, including analgesic and antipyretic products. It manufactures Tylenol® (acetaminophen) brand single-ingredient and combination-ingredient products for adults and children, as well as acetaminophen-containing products under the Sudafed® and Benadryl® brand names for adults. McNeil also markets Motrin® (ibuprofen) products for use by adults and children, as well as St. Joseph® aspirin (81 mg) for use by adults only. As a major manufacturer of OTC drug products, McNeil is committed to encouraging appropriate use and discouraging misuse of its products as well as implementing interventions to help reduce acetaminophen overdose and liver injury while continuing to help ensure appropriate use of all OTC analgesics.

Overview

The Food and Drug Administration (FDA) announced that it will hold a public meeting on June 29 and 30, 2009 and seek advice on what options would be most effective to control the overdoses associated with acetaminophen products, both over-the-counter (OTC) and prescription (Rx).

McNeil agrees with FDA's assessment that acetaminophen is an important drug used to treat pain and fever in both over-the-counter and prescription settings.

> "Acetaminophen is an important drug, and its effectiveness in relieving pain and fever is widely known. Unlike other commonly used drugs to reduce pain and fever (e.g., nonsteroidal antinflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and naproxen), at recommended doses acetaminophen does not cause adverse effects, such as stomach discomfort and bleeding, and acetaminophen is considered safe when used according to the directions on its OTC or Rx labeling"[1].

In the United States, acetaminophen and acetaminophen-containing products are among the most frequently used medications. In any given week, approximately 20% of adults

[1] FDA's background for meeting at
http://www.fda.gov/cder/audiences/acspage/meetings/joint_meeting_dsarm_ndac_aisdac_20090630.htm

report using acetaminophen containing products, and by any measure, adverse events with acetaminophen are very rare.

However, when more than the recommended dose is taken (overdose), liver injury can occur. McNeil is committed to working with FDA and other stakeholders to proactively address and reduce acetaminophen overdose and liver injury in the United States. Acetaminophen associated liver injury is a complex, multi-factorial issue and it requires a thorough understanding of the root causes and associated consumer behaviors to identify appropriate interventions.

McNeil, others in industry, FDA and other stakeholders must work more collaboratively to reduce the incidence of acetaminophen overdose and liver injury, keeping in mind the three specific factors that FDA noted in its options paper: (1) the effect an option would have on prescribers, consumers, and caregivers, including benefits, costs and potentially unintended consequences; (2) how long it would take to implement the option; and (3) the effect an option would have on companies producing or pharmacies dispensing products containing acetaminophen.[2]

Although all of these factors put forth by FDA are valid, McNeil believes the most important factor is the first one. It is critical to keep focus on acetaminophen's unique safety advantages for patients and consumers with certain medical histories and conditions (i.e. elderly, gastrointestinal bleeding, renal disease, cardiovascular disease, hepatic disease, asthma, pregnancy and drug-drug interactions) compared to other OTC analgesics and to consider the impact of FDA options on switching patients and consumers from acetaminophen to NSAIDs with the resulting unintended adverse healthcare outcomes and healthcare costs.

While it is likely that some of the options proposed in CDER's May 27, 2009 Options Paper help address the issue of acetaminophen overdose and liver injury, they may engender

[2] FDA's background for meeting at
http://www.fda.gov/cder/audiences/acspage/meetings/joint_meeting_dsarm_ndac_aisdac_20090630.htm

unintended health consequences. Specifically, some of the options proposed by FDA may encourage individuals to switch from acetaminophen to other OTC analgesics, such as NSAIDs, which have documented serious adverse health effects.

In this briefing book, McNeil provides data on the safety and efficacy of acetaminophen, patient and consumer use, our perspective on FDA's stated options and potential interventions as part of McNeil's proposed risk mitigation framework with the goal of reducing acetaminophen overdose and liver injury.

McNeil Perspective on FDA's Proposed Options

McNeil shares FDA's goal of reducing acetaminophen overdose and liver injury. Given the clinical importance of acetaminophen, any actions intended to address this issue must be appropriately tailored to address the root causes of acetaminophen overdose and liver injury without encumbering drug availability, interfering with the products' benefits or engendering unintended health consequences.

Enhance public education efforts

McNeil fully supports FDA's goal of enhancing public education efforts and agrees that the messages used in such effort should be concise, clear and tested and that improvements can be made. McNeil, as part of the Consumer Healthcare Products Association (CHPA) Task Group on Acetaminophen, is committed to work in concert with FDA, other manufacturers and other stakeholders to expeditiously develop, fund and test the effectiveness of future educational efforts. These educational efforts must be focused on root causes and consumer behaviors and tested to increase the likelihood they will deliver against agreed upon goals. Clear measurements must be aligned to and put into place before these programs begin in order to measure the success of the education.

From 2002 to present, McNeil developed and executed labeling changes and implemented communication and educational initiatives focused on key messages intended to help alter behaviors that may lead to overdose. Examples of these messages include:

- Reading and following the label
- Taking no more than the recommended dose

- Keeping medicine out the reach of children
- Not taking more than one acetaminophen containing product at a given time.

McNeil has put forth significant resources (approximately $55 million) against these initiatives, achieving broad reach and impressions. A recent update of acetaminophen use patterns from the Slone survey suggests that these efforts may have already begun to show some positive impact (see Table 2). McNeil recognizes that despite these significant efforts, in absence of a clear set of agreed upon and pre-defined measurements, the true impact remains uncertain. Furthermore, our experience suggests that future education may be more impactful if it:

- is specifically focused on the behaviors that may lead to overdose
- clearly communicates the risk of liver injury with overdose
- is positioned closer to the actual point of acetaminophen use (i.e., on shelf, on package/bottle).

Improve Labeling

On April 29, 2009, FDA issued its final regulation on labeling for OTC pain relievers and fever reducers, including acetaminophen. Most of these warnings were implemented voluntarily by McNeil, prior to FDA's final rule. McNeil is changing product labeling to comply with the balance of the changes outlined in FDA's final regulation and expects products to be on the retail shelf with this revised labeling later this year.

Reduce current dosage strengths/Restrict current maximum doses to Rx only

McNeil disagrees that the current doses, the 1000 mg single adult dose and the 4000 mg current maximum adult daily dose, of acetaminophen should be reduced or that the 500 mg form change from OTC to prescription status. The safety and efficacy of both the 1000 mg single adult dose and the 4000 mg maximum daily dose has been well established and both provide a needed patient benefit. These doses have a long safety history and have extensive professional endorsements which clearly demonstrate the need for these products. McNeil believes that there are risk reduction opportunities that should be evaluated and implemented with alacrity, before such significant changes as reducing the

current dosage strengths are considered. McNeil is also concerned about unintended consequences that may occur with reducing the dose of acetaminophen.

Additional considerations regarding FDA Option 1a – Reduce current dosage strengths (including the recommended maximum adult daily dose, the single adult dose and dosage strengths in OTC products)

- Data from clinical studies support the 500 mg formulation and the safety and efficacy of the current 1000 mg maximum allowable single dose of acetaminophen. Data from randomized, double-blind, placebo-controlled clinical trials in multiple pain models demonstrate that acetaminophen 1000 mg provides better analgesia compared to the 650 mg dose and the duration of effect of 1000 mg is longer than the duration seen with acetaminophen 650 mg.
- Many patients and consumers require a 1000 mg dose to achieve adequate analgesia. Adequate analgesia is a clinically appropriate goal and one that consumers will likely self titrate to. Another likely alternative to self-titration would be to seek alternate therapy (e.g., OTC NSAIDs) in order to achieve this level of analgesia. As noted previously, such switching could have significant public health consequences.
- The current maximum adult daily dose of up to 4000 mg per day is safe, effective and is the dose healthcare professionals and key medical groups recommend as a first-line treatment for patients with osteoarthritis. The safety and efficacy of acetaminophen for the treatment of pain for extended time periods has been demonstrated in ten osteoarthritis trials. These studies demonstrated that acetaminophen, when taken up to the recommended daily dose of 4000 mg per day, was safe and effective.

Additional Considerations regarding FDA Option 1b – Restrict currently recommended maximum adult daily dose, single adult dose, and dosage form strengths to Rx only status

- Large groups of patients and consumers, including those suffering from cardiovascular disease, patients suffering renal disease and elderly sufferers of musculoskeletal pain who benefit from acetaminophen would have an extremely difficult time accessing the 1000 mg acetaminophen dose.

- Requiring a prescription in order to obtain the 500 mg formulation would inconvenience patients and consumers as well as healthcare professionals and would likely increase patients and consumer costs as well as healthcare system costs, leaving patients and consumers, especially those with more limited access to healthcare, little option but to seek alternatives to acetaminophen.
- Retail pharmacies could potentially be burdened by a high influx of patients and consumers that require pharmacy attention to obtain products formerly available to them over the counter.
- Data exist that demonstrate that when an OTC product is moved to Rx status, its usage falls considerably, as was the case in Oregon with pseudoephedrine, suggesting the potential for significant switching to other alternatives.

Establish package size limits for OTC acetaminophen products

McNeil agrees with FDA's working group that pack size limits should not be established for OTC acetaminophen products, given that the data from the UK is inconclusive, sales restrictions may not be feasible, and that this option may lead to unintended consequences.

Additional considerations:

- Given the conflicting outcome data in the UK and limitations of the available reports, the evidence for public health benefit from OTC acetaminophen package size or package configuration restrictions is not convincing.
- If package size restrictions were mandated for select analgesics, (e.g., only acetaminophen) the potential for unintended consequences resulting from patients and consumers switching to other OTC pain relievers rises considerably.
- In other countries package size is more routinely limited and is done based on duration of use regardless of ingredient. There is no precedent for FDA to mandate such an action in the case of an OTC ingredient; however, if the agency were to do so, it should be done by category regardless of ingredient.

Eliminate combination OTC products that contain acetaminophen

McNeil disagrees that combination OTC products that contain acetaminophen should be eliminated. Acetaminophen overdose and liver injury are infrequently associated with OTC combination products. Combination products are more than just a "convenience for consumers", they have been demonstrated to provide clinical benefit in their combination, they may decrease dosing errors, they reduce pill burden and are a cost-efficient way to deal with multiple symptoms that occur with common illnesses.

Additional considerations:

- Based upon the limited number of cases of acetaminophen overdose and liver injury in children and adults that are attributable to OTC combination products containing acetaminophen, it is unlikely this option would have significant impact.
- Adults experience symptom complexes for which an OTC acetaminophen-containing combination product is beneficial, such as pain with sleeplessness. The combination of acetaminophen and diphenhydramine is commonly used by consumers to treat this problem. Three studies have demonstrated that the combination of acetaminophen 1000 mg and diphenhydramine 50 mg is effective for pain relief, sleep maintenance and quality and was well tolerated.
- Children and adults frequently develop colds and flu with one or more painful symptoms including nasal congestion, sore throat, cough, runny nose, pain, and fever. The majority of these symptoms are experienced concurrently. While consumer use of OTC combination products provides relief of multiple concurrent symptoms, findings from studies of fixed-dose combination-ingredient prescription products, demonstrate improved adherence, reduced pill burden and costs and improved outcomes.
- The use of combination products reduces the likelihood of dosing errors since consumers measure and administer one product, instead of several products, for relief of their symptoms. The use of combination products eliminates the need for the consumer to review, understand and keep track of the dosing and Drug Facts on multiple products, some of which may have different dosing intervals. This simplifies medication administration, thus reducing the opportunity for dosing errors.

- Combination products make it easier to administer treatments to children. Parents and caregivers can use one product to treat multiple symptoms instead of using multiple products. Children are more likely to be compliant with taking one combination product than with taking multiple single-ingredient products.
- If FDA decides that OTC acetaminophen-containing combination products should be eliminated based in part on "occasions when all of the ingredients of the combination product are not needed", then FDA should consider applying this rationale to all OTC analgesic combinations.

Limit dosing formulations for OTC liquid products; require dosing device

McNeil agrees with the FDA Working Group recommendation that dosing instructions for children under 2 years of age be included on the OTC acetaminophen label and provided to healthcare professionals. Dosing instructions for children under 2 years of age have been made available to physicians by McNeil and robust efficacy and safety data exist to support acetaminophen's use in this population. McNeil currently includes a properly calibrated and clearly marked dosing device in each package of liquid medicine, and fully agrees that FDA should make this a requirement for all orally-administered liquid products, regardless of ingredient.

McNeil is concerned about limiting OTC liquid products to one concentration based upon the limited number of reports of acetaminophen overdose and liver injury reported to occur with concentrated drops and because of the multiple potential root causes. McNeil is committed to conducting discussions with leading pediatricians and other stakeholders in order to evaluate the most appropriate next steps. McNeil believes that other interventions, such as the inclusion of dosing instructions for children under 2 years of age, are likely to have a more significant effect on reducing pediatric medication errors leading to acetaminophen overdose.

Additional considerations:

- Concentrated drops are a form recommended preferentially for children under 2 years of age by pediatricians.

- McNeil encourages FDA to permit dosing instructions for children under 2 years of age and that, in doing so, FDA allow dosing instructions on the labeling for concentrated drops *only* for children ages 6 months to 2 years of age. This is consistent with FDA's approved labeling for pediatric ibuprofen concentrated drops and other pediatric ibuprofen-containing liquids.
- Major professional organizations, including American Academy of Family Physicians, American Academy of Pediatrics, American Association of Poison Control Centers and the American Pharmacists Association, have indicated to the FDA in various forums over the years, their support for dosing instructions for children under 2 years of age on OTC acetaminophen products.
- Based upon the limited number of reports of acetaminophen overdose and liver injury in children that are associated with OTC concentrated infants' drops containing acetaminophen, this option is unlikely to have as significant an impact as putting instructions for children under 2 years of age on the label and providing them to health professionals.

FDA Options for Prescription Products

McNeil and Johnson & Johnson Pharmaceutical Research & Development, LLC ("J&J PRD"), which markets prescription acetaminophen-combination products agree that unit-of-use packaging and expanded product warning information for prescription combination drugs may be appropriate in that they are likely to help address the root causes of acetaminophen overdose as currently understood and are unlikely to result in unintended public health consequences. Prescription combination products provide consumer benefit in their synergistic effects and should remain available.

Other Factors for the Advisory Committee to Consider

Use of Acetaminophen

Patients and consumers seeking pain relief or fever reduction should not be denied the opportunity to use the most effective single adult dose and maximum adult dose of acetaminophen that is appropriate for an individual's circumstances and needs when it has been demonstrated that the dose can be used safely. In the United States, acetaminophen and acetaminophen-containing products are among the most frequently used medications.

In any given week, approximately 20% of adults report using acetaminophen containing products. Over-the-counter acetaminophen products are used by consumers for a variety of pain conditions at doses up to 4000 mg per day. For osteoarthritis pain, doses of up to 4000 mg per day are specifically recommended as first line therapy by the American Pain Society (APS), American College of Rheumatology (ACR) and the Agency for Healthcare Research and Quality (AHRQ).

Acetaminophen is the analgesic recommended specifically for use in populations at increased risk for NSAID-related adverse effects, such as the elderly, patients with renal disease and patients with ulcer disease (Table 1).

Table 1: Recommendations For Acetaminophen Use In Special Populations

Organization	Special Population	Acetaminophen Use
American Heart Association	Stroke patients	Fever
	Aspirin for cardioprotection	Pain relief
	CV disease or ischemic heart disease	Musculoskeletal symptoms
	Risk for GI bleeding	Pain relief
American College of Gastroenterology	Patients with Ulcers; chronic pain of arthritis	Pain relief
National Heart, Blood and Lung Institute	Aspirin/NSAID sensitive patients	Fever and Pain relief
American Geriatrics Society	Older persons	Mild to moderate musculoskeletal pain
National Kidney Foundation	Underlying renal disease	Episodic pain relief

Over-the-counter availability of the 4000 mg total daily dose of acetaminophen is an important first-line therapy for the management of osteoarthritis. A change in the OTC availability of the 4000 mg maximum daily dose, a recommended first line treatment for osteoarthritis pain, or a change in the 500 mg formulation and/or 1000 mg dose of acetaminophen, which have been clinically demonstrated to treat pain as well as OTC NSAIDs, could lead to patients and consumers not receiving analgesia with lower doses of acetaminophen. This in turn could result in patients and consumers with certain medical histories and conditions (i.e. elderly, gastrointestinal bleeding, renal disease, cardiovascular

disease, hepatic disease, asthma, pregnancy and drug-drug interactions) shifting to and increasing their use of NSAIDs.

In regards to consumer use patterns of acetaminophen-containing products, The Slone Survey provides tracking of its use by consumers over two discrete time periods of 1998-2001 compared to 2004-2007. The Slone Survey findings (Table 2) show that of consumers who report using acetaminophen-containing products, the vast majority report using one acetaminophen product at a time. The data also show a decline in the use of multiple acetaminophen-containing products at a time. In terms of reported average daily dose of acetaminophen by consumers, the Slone Survey findings continue to show very low percentages of use > 4000mg per day.

Table 2 Slone Survey – Analyses of Data Collected 1998-2001 and 2004-2007 Regarding Use of Acetaminophen in the 7 days Prior to Interview

	1998-2001 (n=6279)	2004-2007 (n=8947)
Number of acetaminophen-containing products taken		
None	78%	81%
One	20%	17%
Two	2.2%	1.6%
Three	0.2%	0.2%
Prescription status of product taken		
OTC only	19%	15%
Rx[a] only	2.2%	2.7%
Both OTC and Rx[a]	0.7%	0.5%
Prevalence of Use of Product Type		
Monopreparation only	12%	9.6%
Monopreparation plus OTC combination product	1.0%	0.8%
Monopreparation plus Rx combination product	0.4%	0.3%
OTC combination product only	6.5%	5.0%
OTC combination plus Rx combination products	0.3%	0.2%
Rx[a] combinations products only	2.2%	2.7%
Monopreparation plus OTC combination products plus Rx[a] combination products	<0.1%	<0.1%
Prevalence of Average Daily Acetaminophen Dose in the Preceding Week		
≤ 2000 mg	15%	13%
2001 - 4000 mg	1.0%	0.7%
> 4000 mg	0.2%	<0.1%
Unknown	5.4%	4.9%
None	78%	81%

[a] Prescription (Rx) acetaminophen-containing products

Relative Efficacy of Acetaminophen and Ibuprofen

While McNeil shares the FDA's goal of reducing the risk of liver injury in consumers who use acetaminophen, seeking to achieve this goal by restricting consumer access to the 1000 mg dose of acetaminophen, would likely result in negative unintended consequences. In such a case, a possible outcome is that suboptimal dosing may cause patients to switch to ibuprofen to potentially obtain improved relative effectiveness and/or increased duration of relief. For many, the switch to ibuprofen would increase their risk of side effects significantly, especially the elderly and those with cardiovascular or renal disease.

Risks Associated with Switching to NSAIDs

The potential for and the consequences of consumers switching to other OTC analgesics must be considered when evaluating options to reduce acetaminophen overdose and liver injury. Chronic use of NSAIDs is associated with significant gastrointestinal, renal and cardiovascular morbidity and mortality. As the FDA working group report states, NSAID gastrointestinal risk is substantial, with deaths and hospitalizations estimated in one publication as 3200 and 32,000 per year, respectively, whereas, the data for acetaminophen overdose and liver injury account for approximately 458 deaths and 26,000 hospitalizations per year, respectively. Given these numbers, it is clear that switching patients from acetaminophen to NSAIDs has the potential to result in significant increased morbidity and mortality. McNeil agrees with FDA's working group, which recognized that, "…NSAIDS, especially with long-term use, result in important gastrointestinal and renal morbidities. The purpose of the interventions is to reduce acetaminophen-related hepatotoxicity, not to decrease appropriate acetaminophen use or drive people to use NSAIDs instead."

FDA regulatory action should be appropriately and narrowly tailored to reduce overdose and encourage proper use of medicines and to minimize switching large numbers of patients and consumers who use acetaminophen appropriately to NSAIDs. While FDA actions may decrease acetaminophen overdose and liver injury, they may increase NSAID-related adverse events.

Marketplace Impact of Removal of 1000 mg Acetaminophen Dose

Limiting access and/or a need to obtain a prescription for currently used dosage strengths with demonstrated efficacy parity to ibuprofen may shift a high volume of consumers away from using acetaminophen based products and into a potentially riskier pattern of using NSAID's for a greater number of pain treatment occasions. The potential for removing the 1000 mg acetaminophen dose is a significant step for FDA to consider taking and would have negative effects on prescribers, consumers, caregivers as well as the companies producing or pharmacies dispensing products.

Proposed Risk Mitigation Framework for Acetaminophen Overdose and Liver Injury

Acetaminophen is one of the most commonly used analgesic and antipyretic drugs in the United States. When used according to dosing instructions, acetaminophen is safe and effective; however, overdose can lead to liver injury.

McNeil is proposing to work collaboratively with FDA and other stakeholders to develop a comprehensive, integrated risk mitigation framework focused on root causes of pediatric and adult acetaminophen overdose and liver injury which would include specific goals, the activities to be undertaken to meet those goals, and the criteria to verify success. In order to maximize program effectiveness, potential interventions to reduce acetaminophen overdose and liver injury should be based upon and targeted to specific root causes of acetaminophen overdose. Analysis of root causes of acetaminophen overdose and liver injury should be focused on:

- product type (OTC vs. Rx, OTC single ingredient vs. OTC combination ingredient)
- age (pediatric vs. adult)
- intent (accidental unsupervised ingestion, therapeutic intent, self-harm)
- dose (overdose, reported therapeutic dose)
- reasons for medication errors occurring with therapeutic intent

This type of analysis provides insights that can be used to develop potential interventions as part of a proposed risk mitigation framework. Where there are gaps or inconsistencies in the understanding of root causes of acetaminophen overdose and liver injury, additional

research and enhanced surveillance would be an important component of the risk mitigation framework.

This proposal includes specific goals, the actions to be taken to meet those goals (including the development of a research agenda in collaboration with external stakeholders to generate data with respect to theoretical at risk populations) and the mechanisms for measuring the impact of the action against the goals. McNeil will work with FDA to define a final, aligned program with specific roles of McNeil, industry, other stakeholders and FDA in the risk mitigation framework initiative. These interactions will finalize and specifically define the expectations and scope of the program. Also addressed will be the importance of expanding the framework beyond the McNeil proposed framework and implemented across all OTC and prescription acetaminophen manufacturers to have the greatest opportunity for impact.

The following is a summary of a draft risk mitigation framework for acetaminophen that is intended to minimize pediatric and adult overdose without encumbering drug availability, interfering with the products' benefits or engendering unintended health consequences. Within this draft, interventions are proposed to address pediatric unintentional overdose, adult unintentional overdose, and adult intentional overdose. The proposals to reduce acetaminophen overdose take into consideration single ingredient and combination ingredient acetaminophen-containing prescription and OTC products. The proposed solutions are targeted to specific age groups and root causes of acetaminophen overdose. The tools to achieve the objectives of the program should be based on information obtained from modified tracking surveys of consumer behavior and use patterns. These tools may include: packaging changes, labeling changes, a targeted education and outreach program as well as evaluations of the likelihood of unintended health outcomes resulting from consumers switching from acetaminophen use to NSAIDs use.

A high level summary of a proposed risk mitigation framework including goals, objectives, tools, and an evaluation plan are followed by the detailed proposed framework.

GOALS: The goals of the risk mitigation framework are:

- To reduce accidental unsupervised ingestions and unintentional medication errors leading to acetaminophen overdose and/or liver injury in infants and children
- To reduce intentional ingestions and unintentional medication errors that lead to acetaminophen overdose and/or liver injury in adults.

OBJECTIVES: The proposed objectives to achieve these goals include:

- Infants and children
    1. Reduce the frequency and severity of accidental unsupervised ingestions with McNeil pediatric liquid acetaminophen formulations in children by 25% within 5 years.
    2. Reduce unintentional medication errors leading to acetaminophen overdose and/or liver injury in infants and children.

- Adults
    1. Better understand the characteristics and usage patterns of OTC and prescription acetaminophen medicines in patients who developed acute liver failure (ALF).
    2. Determine the feasibility of impacting intentional overdose and/or reduction of magnitude of exposure involving OTC acetaminophen containing products in adults.
    3. Reduce unintentional medication errors leading to acetaminophen overdose and liver injury in adults
    4. Reduce concomitant use of single ingredient and combination ingredient acetaminophen-containing prescription and OTC products leading to overdose

TOOLS: The tools and strategies that may be employed to help achieve these objectives include:

- Label and package changes
- Enhanced surveillance and data collection tools
- Targeted education and outreach

- Consumer comprehension testing
- Behavioral research tools

EVALUATION PLAN: The evaluation measurements used to periodically assess the effectiveness of the plans' goals, objectives, strategies and tools will be discussed with FDA and developed and validated to appropriately measure the effectiveness of the proposed interventions. The data collection may come from a variety of new or existing internal and external databases and research programs.

Proposed Risk Mitigation Framework for Acetaminophen-Related Overdose and Liver Injury

Goal 1:	**Reduce Accidental Unsupervised Ingestions and Unintentional Medication Errors Leading to Acetaminophen Overdose and/or Liver Injury in Infants and Children**
Objective 1	**Reduce the frequency and severity of accidental unsupervised ingestions with McNeil's pediatric liquid acetaminophen formulations in children by 25% within 5 years**
Rationale	Data suggest that pediatric liquid acetaminophen formulations account for the majority of accidental unsupervised ingestions with acetaminophen-containing products in children each year
Activity	Packaging a) Add flow regulators on all McNeil pediatric liquid acetaminophen formulations that limit the amount of acetaminophen exposures if the child resistant packaging feature is defeated or is not appropriately reapplied b) Convert all non Child-Resistant (NCR) packages to Child-Resistant (CR) packages for all McNeil acetaminophen-containing products
	Labeling a) Revise labeling per final monograph b) Explore via research opportunities for labeling interventions to address root cause
	Targeted Education and Outreach Program a) Focus on targeted at-risk populations (e.g., parents, caregivers) b) Communication at points of consumption and influence c) Reinforce and enhance message ("Keep out of Reach") to consumers and healthcare professionals
Potential Criteria to Verify Success	Work with FDA, CDC and other stakeholders to define mechanisms to measure success. This would include the requirement to attain adequate baseline information and agreed upon metrics.
	Comprehension testing of educational messages

Goal 1: (cont.)	**Reduce Accidental Unsupervised Ingestions and Unintentional Medication Errors Leading to Acetaminophen Overdose and/or Liver Injury in Infants and Children**
Objective 2	**Reduce unintentional medication errors leading to acetaminophen overdose and/or liver injury in infants and children**
Rationale	Data suggest that caregivers sometimes measure and/or administer incorrect doses to children or give adult medicines to children
Activity	Packaging In-pack validated dosing device (already present in McNeil liquid acetaminophen-containing pediatric products)
	Labeling a) Add dosing directions on OTC label of concentrated/infants products for 6 months to <2 years of age; accordingly limit suspension to 2 years and older; highlight new dosing directions on package b) Establish requirement in "Directions" to use in-pack measuring device c) Standardize dosing abbreviations and volumetric measures for dosing directions
	Targeted Education and Outreach Programs a) Conduct meeting with leading pediatricians and other stakeholders in order to evaluate the most appropriate next steps b) Communicate new "Under 2 dosing directions" to consumers and healthcare professionals c) Evaluate and test enhanced messages ("Don't use adult medicines in children" and "Don't give more than the recommended dose") d) Develop and test appropriate messaging around liver damage warning
Potential Criteria to Verify Success	Reduction in the number of medication errors related to therapeutic intent, resulting in overdose (in internal and external databases - e.g., call centers, surveys, visits to emergency department (ED), poison control center calls, etc.)

Goal 2:	Reduce Intentional Ingestions and Unintentional Medication Errors That Lead to Acetaminophen Overdose and/or Liver Injury in Adults
Objective 1	**Better understand the characteristics and usage patterns of OTC and prescription acetaminophen-containing medicines in patients who developed acute liver failure (ALF)**
Rationale	Data collection is currently limited regarding acetaminophen medications use by patients with ALF
Activity	a) Work with FDA, external stakeholders and others in industry to design and implement an enhanced Surveillance System to augment existing data surveillance tools and/or create data collection processes to better understand clinical and behavioral characteristics individuals with acetaminophen-associated liver injury
	b) Develop research agenda in collaboration with external stakeholders to generate additional data with respect to putative at-risk populations and their potential to develop ALF with currently recommended doses of acetaminophen when used according to the OTC label
Potential Criteria to Verify Success	Implement the enhanced data collection tool in collaboration with external groups in order to establish baseline data within 2 years

Objective 2	**Determine the feasibility of impacting intentional overdose and/or reduction of magnitude of exposure involving OTC acetaminophen-containing products in adults**
Rationale	A significant proportion of acute liver failure cases is associated with acute, intentional acetaminophen overdose
Activity	Packaging Assess the potential for packaging to decrease the magnitude of exposure in the event of impulsive intentional overdose without causing unintended health consequences
	Targeted Education and Outreach Program Communicate appropriate messaging around label warning regarding acetaminophen overdose and liver injury, need for quick medical attention even if no signs/symptoms
Potential Criteria to Verify Success	Meet with FDA to discuss test findings within 1 year
	If packaging is implemented, track overdoses via enhanced surveillance system developed in Objective 1 above

Goal 2: (cont.)	**Reduce Intentional Ingestions and Unintentional Medication Errors That Lead to Acetaminophen Overdose and/or Liver Injury in Adults**
Objective 3	**Reduce unintentional medication errors leading to acetaminophen overdose and/or liver injury in adults**
Rationale	Data suggest that adults sometimes unintentionally take more than the recommended dose
Activity	Determine the target users who exhibit this behavior by using surveys and/or other appropriate methodologies
	Labeling Develop and test optimal methods to communicate acetaminophen as ingredient in OTC and Rx medications
	Targeted Education and Outreach Program a) Reinforce and enhance messages ("Don't take more than the recommended dose") to consumers and healthcare professionals b) Communicate appropriate messaging around liver damage warning
Potential Criteria to Verify Success	Reduction in reporting of dosing in excess of label from monitoring of an appropriate and validated surveillance tool
	Reduction in the number of medication error reports to internal and external databases

Objective 4	**Reduce concomitant use of single ingredient and combination ingredient acetaminophen-containing prescription (Rx) and OTC products leading to overdose and/or liver injury**
Rationale	Some adults report taking more than one product containing acetaminophen at a time
	Data suggest that acetaminophen is not spelled out on all prescription containers and patients are unaware that acetaminophen is in their Rx medication
Activity	Labeling a) Develop and test optimal methods to communicate acetaminophen as ingredient in OTC and Rx medications b) Implement FDA-required packaging and labeling changes for OTC and prescription products
	Targeted Education and Outreach program Reinforce and enhance messages ("Don't take more than one acetaminophen-containing product at the same time") to consumers and healthcare professionals
Potential Criteria to Verify Success	Track the change number of reports (internal and external databases) of overdose involving concomitant use of Rx and OTC acetaminophen containing products.

SECTION 2 OVERVIEW AND KEY POINTS OF BRIEFING BOOK SECTIONS

2 OVERVIEW OF KEY POINTS FROM BRIEFING BOOK SECTIONS

This briefing book provides data on the efficacy and safety of acetaminophen at single doses up to 1000 mg/day and maximum daily doses of doses up to 4000 mg/day, other scientific data on acetaminophen and information on the patient and consumer base of acetaminophen. Selected key points of scientific sections of the briefing book follow.

Efficacy and Safety of Acetaminophen from Clinical Trials – Section 3

- Data from randomized, double-blind, placebo-controlled, single-dose clinical trials demonstrate that acetaminophen 1000 mg provides significantly better analgesia in the general population, compared to the 650 mg or 500 mg dose; the duration of effect of acetaminophen 1000 mg is also longer than the duration seen with acetaminophen 650 mg or 500 mg.
- Meta-analyses support the superior efficacy of acetaminophen 1000 mg compared to acetaminophen 650 mg.
- Pharmacokinetic-pharmacodynamic (PK-PD) modeling shows that acetaminophen 1000 mg consistently exceeds or approaches the plasma concentration needed for 50% of maximum analgesic effect (EC50), whereas acetaminophen 650 mg does not.
- Multiple-dose data demonstrate that the currently labeled maximum daily dose of acetaminophen (3900 to 4000 mg per day) provides significantly better analgesic efficacy, compared with lower doses (1950 to 2000 mg per day), and that this analgesic effectiveness is sustained over time.

Acetaminophen Metabolism, Safety and Threshold Toxicity – Section 4

<u>Metabolism</u>

- Acetaminophen is primarily metabolized by the liver via three pathways: glucuronidation, sulfation, and oxidation. All resulting *conjugates* from these pathways are inactive and nontoxic. Only the sulfation pathway is capacity-limited, as the glucuronide pathway does not saturate, even following a substantial acute acetaminophen overdose.

- The toxic intermediate, NAPQI,
  - is generated by the cytochrome P450 2E1 (CYP2E1) oxidation of acetaminophen;

  - is not measurable due to its high reactivity and instantaneous conjugation and detoxification with *glutathione;*
  - likely initiates a cascade of reactions after a substantial acute overdose resulting in hepatotoxicity.

- Hepatic glutathione (GSH) is
  - present in sufficient quantities to conjugate the small percent of NAPQI produced following therapeutic acetaminophen doses;
  - continuously replenished at an estimated rate of 20 to 30 μmol/min in humans, corresponding to approximately 14 g per day;
  - truly depleted when intracellular concentrations fall below 10% of normal (the critical point at which mitochondria become susceptible to oxidative stress).

- Enhanced glucuronidation with repeat dosing of acetaminophen has been
  - recognized only recently and represents a protective metabolic pathway;
  - demonstrated with repeated administration of 650-mg up to 2000-mg doses;
  - observed in studies of infants, healthy young and older adults, and adults with preexisting liver disease, including cirrhosis and Gilbert's Syndrome

- At this time, research on the evolving science of acetaminophen-protein adducts has confirmed exposure, but not the dose, timing or causal relationship to liver injury.

<u>Safety Data from Ingestions of Repeated Maximum Therapeutic & Supratherapeutic Doses</u>

- Retrospective safety reviews of maximum therapeutic doses
  - observed that long-term use of daily acetaminophen prescribed for chronic rheumatoid disease in 1868 (24%) and 5913 (76%) patients treated with 3000 and 4000 mg per day, respectively, are comparable in terms of safety profile when risk factors are taken into account, even in the elderly
  - observed no Hy's Law cases in 42 controlled clinical trials having ≥ 3000 mg daily doses of acetaminophen with durations of use from two days up to 12 months.

- Safety data from prospective studies of repeated supratherapeutic ingestions:
  - A randomized, placebo-controlled metabolism study of repeated doses totaling 6000 and 8000 mg/day for three days in young adults found increases in the liver's ability

to form the nontoxic glucuronide metabolite, while not increasing the production of thiol metabolites (surrogate for NAPQI).

- A randomized, placebo-controlled clinical trial in older adults with stroke found that repeated doses of 6000 mg/day acetaminophen for three days (n=697) were well tolerated, with only two reports of liver enzyme disturbance and no reports of liver failure.
- A prospective, observational case series of repeated supratherapeutic overdoses suggest that the threshold for hepatotoxicity from repeated supratherapeutic ingestions over two-to-three days may be at least 8000 mg/day.

Threshold for Toxicity in the Pediatric Population

- Children under the age of 6 years are generally considered more efficient in metabolizing acetaminophen and less susceptible to toxicity than older children and adults. The most current view among medical toxicologists is that an acute accidental overdose of greater than 200 mg/kg is thought to be the threshold for toxicity in this population.

Estimation of Threshold Dose for Acetaminophen Toxicity in Subgroups – Section 5

Chronic Alcohol Abusers

- Maximum daily recommended doses (4000 mg/day) of acetaminophen have been shown to be well tolerated by recently abstinent chronic alcohol abusers in a series of five prospective randomized controlled studies with 2-5 days days of exposure.
- Metabolic suppositions rationalizing a lower threshold dose for hepatotoxicity in chronic alcoholics or individuals with preexisting liver disease (who are often chronic alcoholics with liver disease) are often cited without supportive prospective clinical data.
- The chronic alcoholic population has known behaviors, including greater risk of suicide, comorbid substance abuse, impaired judgment, and accidental deaths associated with risk-taking behaviors, that are likely associated with acetaminophen overdoses.

- Chronic alcohol use in association with acetaminophen overdose may be a risk factor for hepatotoxicity due to late presentation and delay in antidote treatment.

Pre-Existing Liver Disease

- New and published pharmacokinetic studies show that individuals with liver disease have a modest increase in the elimination half-life of acetaminophen (about 1 to 2 h on average) that does not lead to progressive accumulation of acetaminophen with repeat dosing.
- While body clearance is about 15% to 60% lower on average, which reflects slower acetaminophen removal, this is not relevant to the biotransformation to metabolites, which has been shown across multiple studies to be essentially the same as that in healthy adults.
- Importantly, new and published metabolism data in individuals with and without liver disease show that the amount of thiol metabolites (a surrogate marker of NAPQI[1] formation) is similar, demonstrating no decrease in glutathione conjugation or increase in metabolism by CYP2E1 in individuals with liver disease.
- Acetaminophen metabolism by glucuronidation (a nontoxic metabolic pathway) increases with repeated 1000 mg doses up to 4000 mg/day for four days in individuals with diseased and healthy livers. Consecutive daily dosing induces glucuronidation, resulting in increased body clearance of acetaminophen and increased production of the glucuronide metabolite.

Acetaminophen Use and Dosing Instructions in Children <2 Years of Age – Section 6

- McNeil agrees with FDA's recommendation that dosing instructions be included for acetaminophen products intended for use in children 6 months to <2 years of age. Motrin Infants' drops have been in the marketplace for over 10 years with labeling for children 6 months to <2 years of age and parents and caregivers have used this product as directed.
- There is a medical and consumer need for acetaminophen pediatric products for children under the age of 2 years as evidenced by the volume of calls received by

[1] NAPQI (N-acetyl-*p*-benzoquinoneimine) is a highly reactive intermediate, which is conjugated with glutathione to produce the inert, nontoxic thiol metabolites: cysteine, mercapturate, methylthioacetaminophen, and methanesulfinylacetaminophen.

the McNeil Consumer Healthcare Consumer Care Call Center, where a majority of the calls (68%) were for children < 2 years. In contrast, the calls for Children's Motrin with labeling for children down to 6 months of age were evenly distributed across age groups.

- Currently marketed products provide a range of options to consumers, including concentrated drops that are preferred by pediatricians, parents and caregivers of children <2 years of age.
- The considerable body of pulished and unpublished clinical data demonstrate the efficacy and safety of pediatric acetaminophen dosing for the management of fever and mild to moderate pain in children < 2 years of age.
- Many single- and multiple-dose pharmacokinetic and metabolism studies support the doses and dosing regimens proposed for use, through quantitative analysis of pharmacokinetic (and pharmacodynamic, efficacy, or safety) data.
- Incorporating dosing instructions for children 6 months to < 2 years of age targets a root causes of medication errors in this age population including administering greater than the labeled dose and administering concentrated pediatric drops (100 mg/mL) at the dose of the children's suspension liquid (32 mg/mL).

Consumer Need for OTC Combination Medicines – Section 7

- Adults use the combination of acetaminophen and diphenhydramine to treat pain with sleeplessness as it is effective in the treatment of both symptoms and is well tolerated.
- The use of combination medicines reduces the likelihood of dosing errors since patients and consumers administer one medicine, instead of several medicines, for relief of all of their symptoms. The use of combination medicines eliminates the need for the consumer to review and understand the dosing and Drug Facts on multiple medicines, some of which may have different dosing intervals. This simplifies medication administration, thus reducing the opportunity for dosing errors.
- Single ingredient and combination-ingredient cough and cold medicines have similar safety profiles with a very rare occurrence of serious adverse events.

Understanding Root Causes of Acetaminophen Overdose Leading to Liver Injury– Section 8

In order to maximize effectiveness, potential interventions to reduce acetaminophen overdose and liver injury should be based upon and targeted to specific root causes of acetaminophen overdose. Review of cases from the company post-marketing safety database reveal the following:

Product

- McNeil data are consistent with data from the ALF Study Group in that both OTC and prescription medicines contribute to acetaminophen overdose and liver injury.
- McNeil's data are consistent with data from the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) in that OTC combination ingredient acetaminophen containing medicines represent a small percentage of all cases.

Age

- McNeil's data are consistent with data from the ALF Study Group in that the vast majority of patients who develop liver injury are adults.

Intent

- Reported intent may not adequately characterize the actual intent of the patient at the time of acetaminophen exposure.

Pediatric Population

- McNeil's data are consistent with data from the AAPCC NPDS in that accidental unsupervised ingestions are an important root cause of acetaminophen exposures.
- Root causes of medication errors include administering greater than the labeled dose, administering concentrated infants' drops (100 mg/mL) at the dose of the childrens' suspension liquid (32 mg/mL), administering an adult medicine to a child, concomitant use of multiple OTC acetaminophen-containing medicines, and administering acetaminophen more frequently than labeled.

Adult Population

- McNeil's data are consistent with data from the AAPCC NPDS in that self-harm is the most frequently reported root cause of overdose and liver injury.

- Root causes of medication errors include taking greater than the labeled dose, concomitant use of prescription and OTC acetaminophen-containing medicines, concomitant use of multiple OTC acetaminophen-containing medicines, and taking acetaminophen more frequently than labeled.

Dose

- Reported dose ingested may not necessarily be the actual dose ingested.
- McNeil's data are consistent with the ALF Study Group in that most reports in children and adults involve reported overdose.

Estimates and Consequences of Switching from Acetaminophen to NSAIDS – Section 9

- The potential for and the consequences of patients and consumers switching to other OTC analgesics should be considered when evaluating options to reduce acetaminophen overdose.
- Elimination of the acetaminophen 1000 mg dose will likely drive some current acetaminophen users to NSAID use.
- Available data suggest that switching from use of acetaminophen to NSAIDs may result in more people dying from NSAID-associated gastrointestinal bleeding and renal failure than those potentially spared from acetaminophen-associated liver injury.

Consumer Need for and Medical Benefit for Acetaminophen – Section 10

- In the United States (US), acetaminophen-containing products (over-the-counter [OTC] and prescription) are among the most frequently used medications. In any given week, some 19-23% of adults report using acetaminophen-containing products.
- Recent medication use surveys suggest that the vast majority of consumers report using acetaminophen within the labeled OTC daily dose.
- Acetaminophen is the most commonly recommended OTC analgesic in the US. Physicians recommend acetaminophen more commonly than ibuprofen and aspirin for numerous indications, including cold/flu, non rheumatoid arthritis, traumatic pain, post-surgical pain, and headaches.
- Osteoarthritis (OA) causes pain in many Americans and the prevalence of this condition is expected to increase with the increasing age of the population.

- Consumer use of acetaminophen is supported by professional associations recommending OTC acetaminophen at doses of up to 4000 mg per day for conditions such as OA, headaches, and cancer pain. Additionally, acetaminophen is recommended as the OTC analgesic of choice for specific subpopulations at risk for nonsteroidal anti-inflammatory drug (NSAID)-associated gastrointestinal, cardiovascular, or renal adverse effects.

Package Size and Package Configuration Restrictions – Section 11

- Given the conflicting outcome data in the UK and limitations of the available reports, the evidence for public health benefit from OTC acetaminophen package size or package configuration restrictions is not convincing.
- While package sizes and configurations vary worldwide, within a country there are similar package sizes and configurations for all OTC analgesics.
- If package size restrictions were mandated for selected OTC analgesics, eg, only required for acetaminophen, the potential for and the consequences of patients and consumers switching to other OTC drugs should be considered.

SECTION 3 EFFICACY AND SAFETY OF ACETAMINOPHEN FROM CLINICAL TRIALS

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3 EFFICACY AND SAFETY OF ACETAMINOPHEN FROM CLINICAL TRIALS

3.1 FDA's Areas of Concern

FDA has proposed reducing current dosage strengths of acetaminophen (including the recommended maximum adult daily dose, and the single adult dose and dosage strengths in OTC and prescription medicines) as Option 1a in the document titled, Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury, included in FDA's May 22, 2009 background package for the June 29-30, 2009 joint advisory committee meeting. FDA states that the intended effect is to "reduce the single and cumulative doses of acetaminophen to which consumers are exposed, thus decreasing the potential for exceeding the toxic threshold of the drug that could cause liver injury".

3.2 Overview of Efficacy and Safety

The ability of patients and consumers to self-treat pain with acetaminophen and reliably obtain adequate pain relief depends upon the continued availability of OTC acetaminophen-containing medicines that are labeled at the current maximum single dose of 1000 mg[1], as well as at the current maximum daily dose of 4000 mg. Data from clinical trials demonstrate that 1) the 1000 mg single dose provides greater analgesia and antipyretic efficacy, as well as duration of effect, across the entire population, compared with the 650 or 500 mg dose; and 2) that the current maximum daily acetaminophen dosage of 4000 mg/day has a favorable safety profile.

Historically, OTC internal analgesics have been available in a range of doses to facilitate a consumer's choice based on their medical needs and preferences. Based on the data, acetaminophen should not only continue to be available as 1000 mg (extra-strength) dosed every 4 to 6 hours up to 4000 mg per day but also as 650 mg (regular-strength) dosed every 4 hours up to 3900 mg per day, and as 1300 mg (extended-release) dosed every 8 hours up to 3900 mg per day[2]. All of these are equivalent in that they yield similar maximum daily dosages but with different dosing patterns. While lower doses of acetaminophen (650 mg and 500 mg) work for some individuals, other individuals require higher doses (1000 mg) to achieve adequate analgesia. A patient or consumer seeking

[1]According to the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) drug products, the current maximum allowable single adult dose for acetaminophen products is 1000 mg, not to exceed 4000 mg per day (53 FR 46204).

[2] Marketed under approved New Drug Application (NDA)

pain relief or fever reduction should not be denied the opportunity to use the most effective dose of acetaminophen that is appropriate for the individual consumer's circumstances and needs, when it has been demonstrated that acetaminophen can be safely used at the individual dose of 1000 mg as well as up to the maximum labeled daily dose of 4000 mg.

3.3 Key Points

- More than 110 clinical trials conducted over five decades document the efficacy and safety of acetaminophen at currently labeled dosages as a pain reliever and fever reducer.
- Data from randomized, double-blind, placebo-controlled, single-dose clinical trials demonstrate that acetaminophen 1000 mg provides significantly better analgesia in the general population, compared to the 650 mg or 500 mg dose; the duration of effect of acetaminophen 1000 mg is also longer than the duration seen with acetaminophen 650 mg or 500 mg.
- Meta-analyses support the superior efficacy of acetaminophen 1000 mg compared to acetaminophen 650 mg.
- Pharmacokinetic-pharmacodynamic (PK-PD) modeling shows that acetaminophen 1000 mg consistently exceeds or approaches the plasma concentration needed for 50% of maximum analgesic effect (EC_{50}), whereas acetaminophen 650 mg does not.
- Multiple-dose data demonstrate that the currently labeled maximum daily dose of acetaminophen (3900 to 4000 mg per day) provides significantly better analgesic efficacy, compared with lower doses (1950 to 2000 mg per day), and that this analgesic effectiveness is sustained over time.
- Data from controlled clinical trials demonstrate that acetaminophen is well tolerated with a favorable safety profile at dosages up to 4000 mg per day.

3.4 Introduction

Acetaminophen has been available as an over-the-counter (OTC) analgesic and antipyretic in the US since 1955. The efficacy of acetaminophen has been clearly established in a multitude of controlled, single- and multiple-dose clinical studies. The safety profile of therapeutic doses from these clinical studies and from actual patient and consumer experience demonstrates a long record of safety and tolerability.

In this section, the efficacy and safety of therapeutic doses of acetaminophen, as demonstrated in controlled clinical trials, will be reviewed. Data supporting the therapeutic

importance of the current maximum allowable single dose of 1000 mg[3], and the current maximum allowable daily dose of 4000 mg in treating mild-to-moderate pain will be presented.

3.5 Benefits of the Appropriate Acetaminophen Dosing in the Self-Management of Pain

Pain is pervasive among US adults: 89% experience pain at least once a month, approximately half report continuous or intermittent pain that last longer than three months, and 42% experience pain on a daily basis [1, 2]. Individuals experiencing pain almost always rely on self-management in the form of OTC analgesics [3]. The availability of effective OTC analgesics for the treatment of pain allows patients and consumers to make a decision to self-manage pain in a safe and cost-effective manner, especially in situations where immediate access to a healthcare provider may be limited.

Pain is an almost ubiquitous experience. Among the most common painful conditions are headaches, minor pain of arthritis, low back pain, muscle pain, menstrual pain and neck pain and these conditions form the basis for the OTC analgesic indication. For decades, acetaminophen has been a mainstay among choices available to patients and consumers seeking pain relief and/or fever reduction. As shown in this document, acetaminophen 1000 mg has clear evidence of effectiveness in treating a variety of painful conditions; the acetaminophen maximum daily dose of 4000 mg (and dosages above this, as well) has been prospectively shown to be efficacious and to have an excellent safety profile. Additionally, data from controlled clinical trials involving different pain states and data from meta-analyses demonstrate the superior efficacy of 1000 mg compared with lower doses [14-17,113,124, 128-131,134-136].

Under-treatment of pain can result in considerable costs to individuals (eg, the deterioration of physical and psychological health), families (eg, increased social isolation and caregiver distress), employers, and the US healthcare system (eg, substantial healthcare utilization and costs) [3-10]. Limiting the ability of patients and consumers to adequately self-treat pain by compromising the effectiveness of acetaminophen by either decreasing the current allowable maximum single dose of 1000 mg, or the current allowable maximum daily dose

[3] According to the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) drug products, the current maximum allowable single adult dose for acetaminophen products is 1000 mg, not to exceed 4000 mg per day (53 FR 46204).

of 4000 mg, may have a significant negative impact on patients, families, employers, and even the US healthcare system.

3.6 Controlled Clinical Trials in Adults Demonstrate the Efficacy of Acetaminophen

The published literature and McNeil's internal studies include more than 110 placebo-controlled trials that have proven acetaminophen's efficacy in a variety of pain models: dental pain, tension headache/migraine, osteoarthritis, menstrual pain, muscle aches and pains, and fever. This section provides more specific information about these studies and about the range of acetaminophen doses that have been examined, all of which support McNeil's position that maintaining the current maximum allowable single dose, 1000 mg, as well as at the current maximum allowable daily dose, 4000 mg per day, is needed to provide adequate analgesia and antipyretic efficacy, as well as adequate duration of effect, across the *entire* population.

3.6.1 Dental Pain

Seventy-two studies demonstrated the significant analgesic efficacy of acetaminophen, compared to placebo, in a dental pain model [11-13, 16-85]. The dose of acetaminophen studied ranged from 325 mg to 2000 mg, with the majority of studies using 1000 mg.

3.6.2 Muscle Pain

One study by Schachtel demonstrated a significant effect of acetaminophen 650 mg, compared to placebo, in the relief of myalgia in subjects with febrile upper respiratory tract infections and muscle pains [86].

3.6.3 Headache

Fifteen single-dose studies demonstrated the significant effect of acetaminophen, compared to placebo, in treating headache pain [87-101]; thirteen of these studies examined acetaminophen 1000 mg; two studies [87, 91] examined acetaminophen 650 mg and 648 mg, respectively.

Four other clinical studies demonstrated the significant effect of acetaminophen 1000 mg, compared to placebo, in the treatment of migraine [102-105].

3.6.4 Adult Menstrual Cramps

Two studies demonstrated the superior efficacy of acetaminophen 2600 mg per day [106] and 4000 mg per day [107], compared to placebo, in relieving menstrual pain.

3.6.5 Adult Fever

Four studies [86, 108-110] demonstrated the significant effect of acetaminophen 650 mg and two studies [111, 112] demonstrated the significant effect of acetaminophen 1000 mg, compared to placebo, in treating fever in adults.

3.6.6 Osteoarthritis Pain

The safety and efficacy of acetaminophen at current maximum allowable single dose, 1000 mg and the current maximum allowable daily dose, 4000 mg/day has been demonstrated in multiple osteoarthritis studies [113-122]. Acetaminophen is recommended by professional guidelines as a first-line therapy for osteoarthritis.

The safety and efficacy of acetaminophen for treating osteoarthritis pain for greater than ten days under the direction of a healthcare provider has been demonstrated in ten placebo- or NSAID-controlled osteoarthritis trials involving approximately 1200 patients treated with acetaminophen [113-122]. Acetaminophen's efficacy was consistently significantly better than placebo or similar to the NSAID across these studies, in which the duration of treatment ranged from two to 52 weeks.

3.7 Multiple Studies in Different Pain States Demonstrate the Superior Efficacy of 1000 mg vs Either 650 mg or 500 mg

Data from controlled clinical trials involving different pain states and data from meta-analyses demonstrate the superior efficacy of 1000 mg compared with lower doses [13-16,112,123,127-130,133-135].

3.7.1 Individual Clinical Studies Show That Acetaminophen 1000 mg is a Significantly More Effective Dose Than 650 mg

This section provides data from nine studies comparing the efficacy of acetaminophen 1000 mg to that of acetaminophen 650 mg. These nine studies are briefly summarized in Table 3-1.

Table 3-1. Summary of Clinical Studies Comparing the Efficacy of Acetaminophen 1000 mg to Acetaminophen 650 mg

Study	Study Population	Acetaminophen Efficacy Results
Hopkinson (NDA 17-053)	Episiotomy pain	1000 mg > 650 mg 1000 mg and 650 mg > placebo
Bare (NDA 17-053)	Episiotomy pain	1000 mg > 650 mg 1000 mg and 650 mg > placebo
Posatko (NDA 17-053)	Episiotomy pain	Study terminated early. No individual study summary data are available.
Wallach (NDA 17-053)	Episiotomy pain	Strong placebo response No treatment effect
Combined analysis of Hopkinson, Bare, and Posatko (Hopkinson et al 1974) [127]	Episiotomy pain	1000 mg > 650 mg 1000 mg and 650 mg > placebo
80-223 [129]	Dental pain	Moderate baseline pain – 650 mg > placebo Severe baseline pain – 1000 mg > 650 mg 1000 mg and 650 mg > placebo
80-214 [130]	Dental pain	Moderate baseline pain – 1000 mg and 650 mg > placebo Severe baseline pain – 1000 mg > 650 mg 1000 mg and 650 mg > placebo
82-224 [131]	Dental pain	1000 mg and 650 mg > placebo
80-210 [132]	Episiotomy pain	No treatment effect
Yuan et al 1998 [128]	Induced pain (cold pressor test)	Dose-related effect reported (model main effect) 1000 mg > placebo (pair-wise)

In NDA 17-053 submitted to the FDA for approval of Tylenol 500 mg tablets, four studies evaluated acetaminophen 1000 mg and acetaminophen 650 mg compared to placebo. The results of all four studies (Hopkinson, Bare, Posatko, Wallach) are presented in detail individually in Sections 3.7.1.1 through 3.7.1.4 in the way they were summarized in the original reports. Two of these studies (Hopkinson, Bare) showed that acetaminophen 1000 mg was superior to acetaminophen 650 mg and that acetaminophen 1000 mg and acetaminophen 650 mg were statistically significantly superior to placebo. The combined analysis of three studies from the NDA was published [127] and is presented in Section 3.7.1.5.

One other published placebo-controlled study specifically compared acetaminophen 1000 mg and 650 mg and demonstrated that 1000 mg was directionally more effective than 650 mg [128] and is presented in Section 3.7.1.7. In addition to published studies, two studies [129, 130] demonstrated that acetaminophen 1000 mg provided noticeable benefit at higher levels of pain, ie, acetaminophen 1000 mg was statistically significantly superior to acetaminophen 650 mg for analgesia in subjects with severe, but not moderate, initial pain. Two studies [131, 132] did not show significant difference between acetaminophen 1000 mg and 650 mg. These four studies are presented in Section 3.7.1.6. However, none of these nine studies were included in the original meta-analysis or updates by McQuay and colleagues [133-135] described in Section 3.7.3.

3.7.1.1 Study by Dr. Hopkinson

This randomized, double-blind, placebo-controlled, single-dose study evaluated acetaminophen 1000 mg, acetaminophen 650 mg, and placebo over a four-hour period in 150 hospitalized postpartum subjects suffering from moderately severe to very severe pain due to an episiotomy (NDA 17-053). Table 3-2 presents the demographic and baseline characteristics of the 150 female subjects. The mean age was 26.8 y, 27.7 y, and 27.5 y in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively and ranged from 16 to 40 y. The baseline pain intensity prior to treatment was similar across the three groups.

Table 3-2. Demographic and Baseline Characteristics - Dr. Hopkinson's Study

Characteristic	Acetaminophen 1000 mg N=50	Acetaminophen 650 mg N=50	Placebo N=50
Age, y			
Mean (Range)	26.8 (16-40)	27.7 (16-40)	27.5 (19-40)
Weight, lbs			
Mean (Range)	149.2 (132-207)	150.3 (123-251)	148.0 (115-219)
Pain Intensity			
Moderately Severe	15	19	23
Severe	24	19	19
Very Severe	11	12	8

Figure 3-1 presents the change in mean pain severity by time. Acetaminophen 1000 mg-treated subjects had significantly ($p<0.01$) lower levels of pain intensity compared to acetaminophen 650 mg-treated subjects. In addition, both acetaminophen 1000 mg-treated subjects and acetaminophen 650 mg-treated subjects had significantly ($p<0.01$) lower levels of pain compared to placebo-treated subjects.

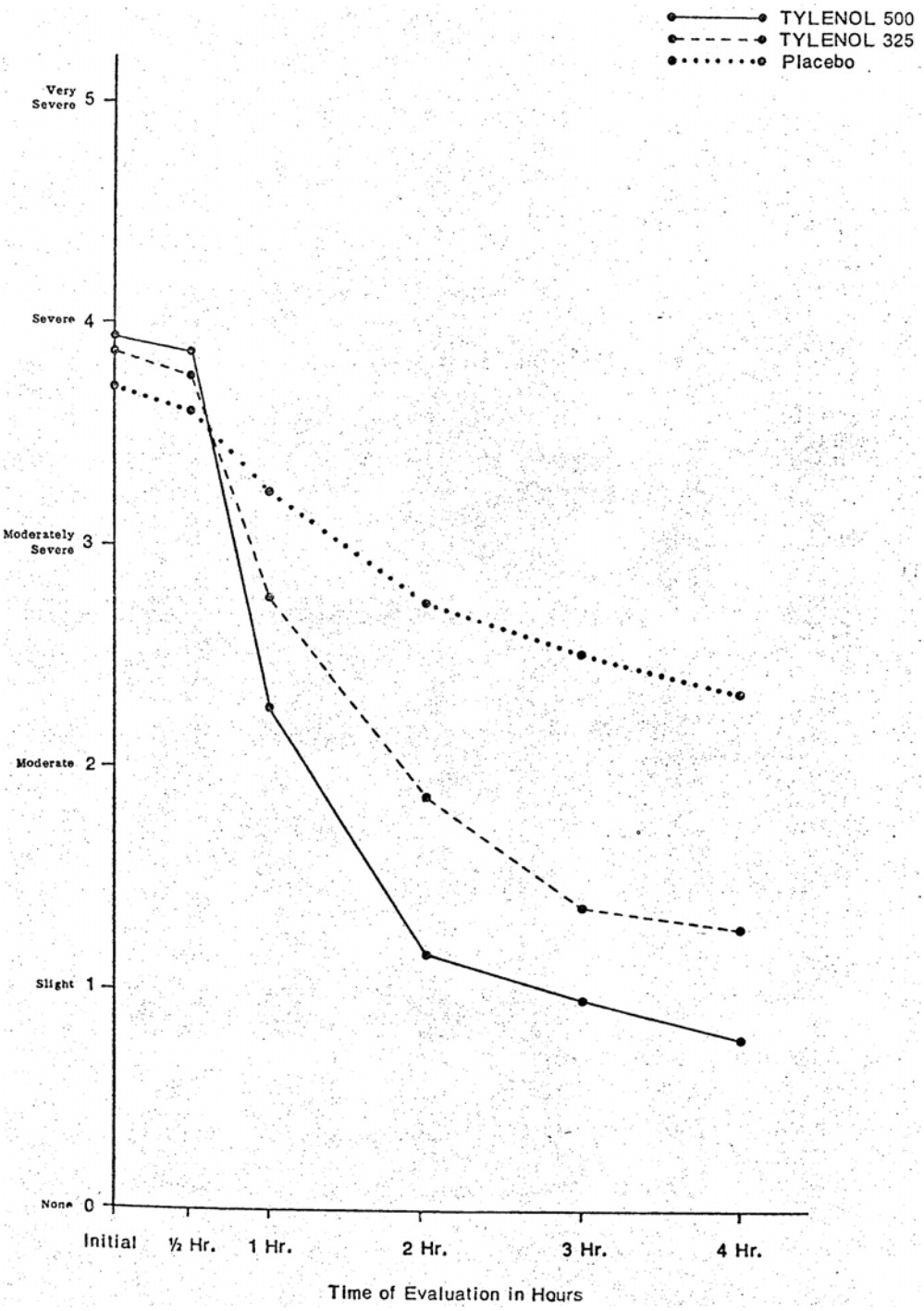

Figure 3-1. Change in Mean Pain Severity by Time - Dr. Hopkinson's Study

Note: TYLENOL 500 corresponds to a 1000 mg dose and TYLENOL 325 corresponds to a 650 mg dose

Acetaminophen 1000 mg-treated subjects had significantly ($p<0.01$) greater pain relief compared to acetaminophen 650 mg-treated subjects. In addition, both acetaminophen 1000 mg-treated subjects and acetaminophen 650 mg-treated subjects had significantly ($p<0.01$) greater pain relief compared to placebo-treated subjects.

The percent of subjects requiring supplemental analgesic medication was 8% (4/50) with acetaminophen 1000 mg, 14% (7/50) with acetaminophen 650 mg, and 44% (22/50) with placebo. Both acetaminophen 1000 mg and acetaminophen 650 mg were statistically significantly different ($p<0.01$) from placebo with no significant difference between the two acetaminophen doses.

Table 3-3 presents a summary of the subject's ratings for global evaluation. The percent of subjects with a rating of excellent or good was 82%, 58%, and 24% in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively.

Table 3-3. Summary of Ratings for Global Evaluation - Dr. Hopkinson's Study

Evaluation	Acetaminophen 1000 mg N=50	Acetaminophen 650 mg N=50	Placebo N=50
Excellent	22	12	4
Good	19	17	8
Fair	6	9	4
Poor	2	5	12
No effect	1	7	22

3.7.1.2 Study by Dr. Bare

This randomized, double-blind, placebo-controlled, single-dose study evaluated acetaminophen 1000 mg, acetaminophen 650 mg, and placebo over a four-hour period in 75 hospitalized postpartum subjects suffering from moderately severe to very severe pain due to an episiotomy (NDA 17-053). Table 3-4 presents the demographic and baseline characteristics of the 75 female subjects. The mean age was 23.9 y, 23.8 y, and 22.8 y in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively and ranged from 19 to 39 y. In each of the three groups, more subjects rated their baseline pain intensity prior to treatment as severe or very severe.

Table 3-4. Demographic and Baseline Characteristics - Dr. Bare's Study

Characteristic	Acetaminophen 1000 mg N=25	Acetaminophen 650 mg N=25	Placebo N=25
Age, y			
Mean (Range)	23.9 (19-39)	23.8 (19-34)	22.8 (20-34)
Weight, lbs			
Mean (Range)	135.6 (126-151)	135.0 (123-157)	133.7 (123-147)
Pain Intensity			
Moderately Severe	2	0	3
Severe	5	6	11
Very Severe	18	19	11

Figure 3-2 presents the change in mean pain severity by time. Acetaminophen 1000 mg-treated subjects had significantly ($p<0.01$) lower levels of pain intensity compared to acetaminophen 650 mg-treated subjects. In addition, both acetaminophen 1000 mg-treated subjects and acetaminophen 650 mg-treated subjects had significantly ($p<0.01$) lower levels of pain compared to placebo-treated subjects.

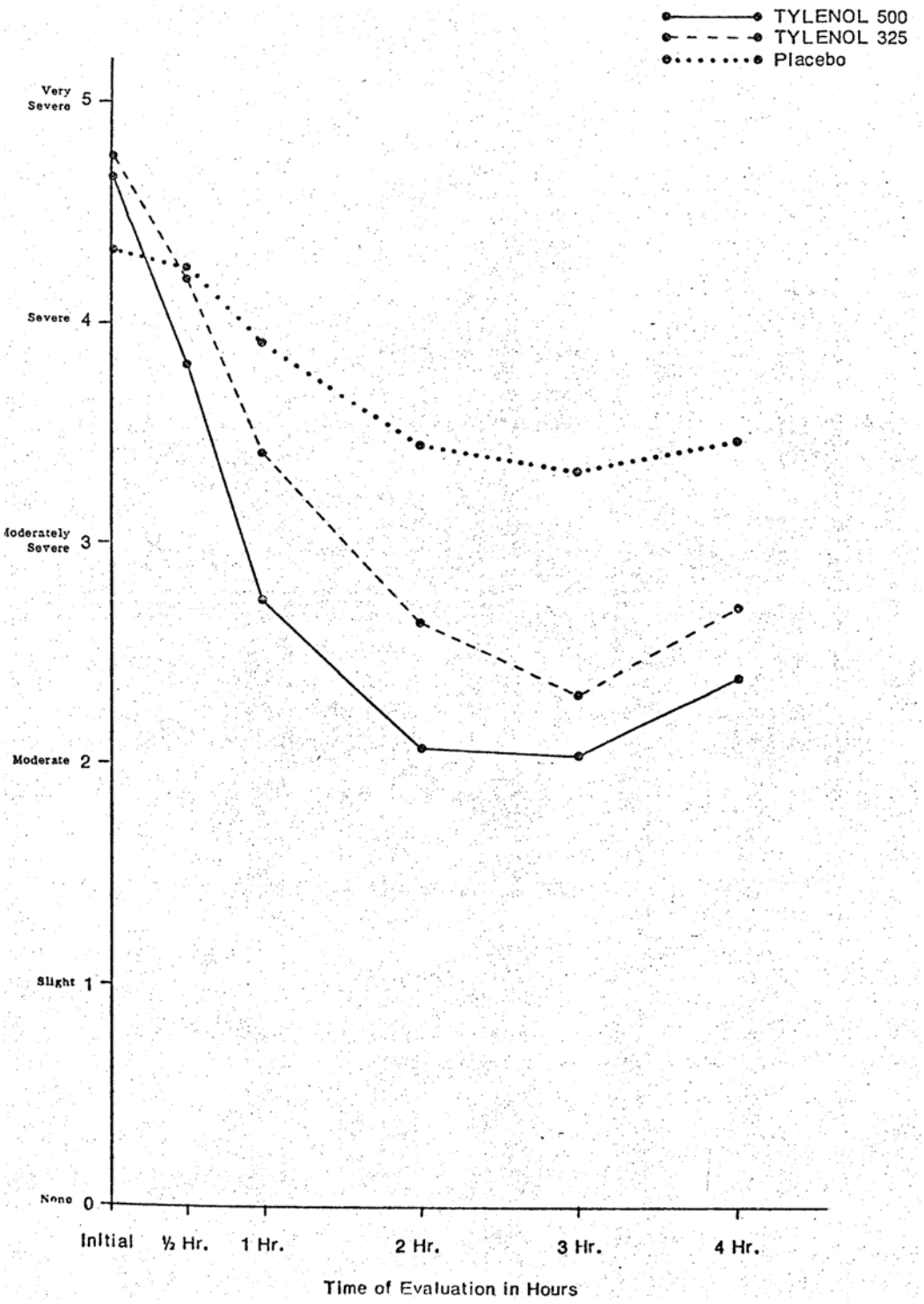

Figure 3-2. Change in Mean Pain Severity by Time - Dr. Bare's Study

Note: TYLENOL 500 corresponds to a 1000 mg dose and TYLENOL 325 corresponds to a 650 mg dose

Both acetaminophen 1000 mg-treated subjects and acetaminophen 650 mg-treated subjects had significantly ($p<0.01$) greater pain relief compared to placebo-treated subjects. Acetaminophen 1000 mg-treated subjects had greater pain relief compared to acetaminophen 650 mg-treated subjects, but this was not statistically significant.

The percent of subjects requiring supplemental analgesic medication was 4% (1/25) with acetaminophen 1000 mg, 8% (2/25) with acetaminophen 650 mg, and 28% (7/25) with placebo. Acetaminophen 1000 mg was statistically significantly different ($p<0.05$) from placebo. No statistically significant differences were observed between acetaminophen 650 mg and acetaminophen 1000 mg or placebo.

Table 3-5 presents a summary of the subject's ratings for global evaluation. The percent of subjects with a rating of excellent or good was 80%, 48%, and 4% in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively. Acetaminophen 1000 mg was significantly ($p<0.01$) superior to acetaminophen 650 mg and placebo. In addition, acetaminophen 650 mg was significantly ($p<0.01$) superior to placebo.

Table 3-5. Summary of Ratings for Global Evaluation - Dr. Bare's Study

Evaluation	Acetaminophen 1000 mg N=25	Acetaminophen 650 mg N=25	Placebo N=25
Excellent	5	3	0
Good	15	9	1
Fair	4	8	5
Poor	0	3	10
No effect	1	2	9

3.7.1.3 Study by Dr. Posatko

This randomized, double-blind, placebo-controlled, single-dose study evaluated acetaminophen 1000 mg, acetaminophen 650 mg, and placebo over a four-hour period in hospitalized postpartum subjects suffering from moderately severe to very severe pain due to an episiotomy (NDA 17-053). Overall, 38 subjects were included in this study with 12 subjects randomized to acetaminophen 1000 mg, 13 subjects randomized to acetaminophen 650 mg and 13 subjects randomized to placebo. This investigator had difficulty enrolling subjects and the study was terminated early. The data from this study were not presented separately in a study report or NDA, but were incorporated into a

combined analysis with the data from the studies by Dr. Hopkinson and Dr. Bare and the results are presented in Section 3.7.1.5.

3.7.1.4 Study by Dr. Wallach

This randomized, double-blind, placebo-controlled, single-dose study evaluated acetaminophen 1000 mg, acetaminophen 650 mg, and placebo over a four-hour period in 75 hospitalized postpartum subjects suffering from moderately severe to very severe pain due to an episiotomy (NDA 17-053). Table 3-6 presents the demographic and baseline characteristics of the 75 female subjects. The mean age was 23.6 y, 22.7 y, and 23.9 y in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively and ranged from 15 to 39 y. The baseline pain intensity prior to treatment was similar across the three groups.

Table 3-6. Demographic and Baseline Characteristics - Dr. Wallach's Study

Characteristic	Acetaminophen 1000 mg N=25	Acetaminophen 650 mg N=25	Placebo N=25
Age, y			
Mean (Range)	23.6 (15-39)	22.7 (17-32)	23.9 (16-36)
Weight, lbs			
Mean (Range)	136.9 (92-220)	143.4 (102-180)	145.9 (105-230)
Pain Intensity			
Moderately Severe	7	11	9
Severe	10	7	13
Very Severe	8	7	3

The percent of subjects requiring supplemental analgesic medication was 0% (0/25) with acetaminophen 1000 mg, 4% (1/25) with acetaminophen 650 mg, and 0% (0/25) with placebo. An analysis of the data obtained in this study was compared with those obtained in similar analgesic evaluations performed earlier and unlike the other studies the placebo response was essentially the same as that for the two doses of acetaminophen.

Table 3-7 presents a summary of the subject's ratings for global evaluation. The percent of subjects with a rating of excellent or good was 80%, 76%, and 80% in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively.

Table 3-7. Summary of Ratings for Global Evaluation - Dr. Wallach's Study

Evaluation	Acetaminophen 1000 mg N=25	Acetaminophen 650 mg N=25	Placebo N=25
Excellent	13	17	11
Good	7	2	9
Fair	3	0	4
Poor	2	3	1
No effect	0	3	0

3.7.1.5 Combined Analysis of Drs. Hopkinson, Bare, and Posatko

The results of the three studies submitted to NDA 17-053 in support of the efficacy of acetaminophen 1000 mg were published by Hopkinson et al [127]. Data from a combined analysis of these three studies was also included in NDA 17-053. These three studies were single-dose, double-blind, randomized, placebo-controlled episiotomy pain studies in 263 subjects, comparing acetaminophen 650 mg and 1000 mg. There were 87, 88, and 88 subjects randomized to acetaminophen 1000 mg, acetaminophen 650 mg, and placebo, respectively. The mean age was 25.8 y, 25.9 y, and 25.8 y in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively and ranged from 16 to 40 y.

A summary of the change in pain severity over time is presented in Figure 3-3. Acetaminophen 1000 mg was statistically significantly ($p<0.01$) superior to acetaminophen 650 mg and both were statistically significantly ($p<0.01$) superior to placebo in reducing pain severity throughout the four-hour study period. Pain severity was reduced more rapidly with acetaminophen 1000 mg compared to acetaminophen 650 mg.

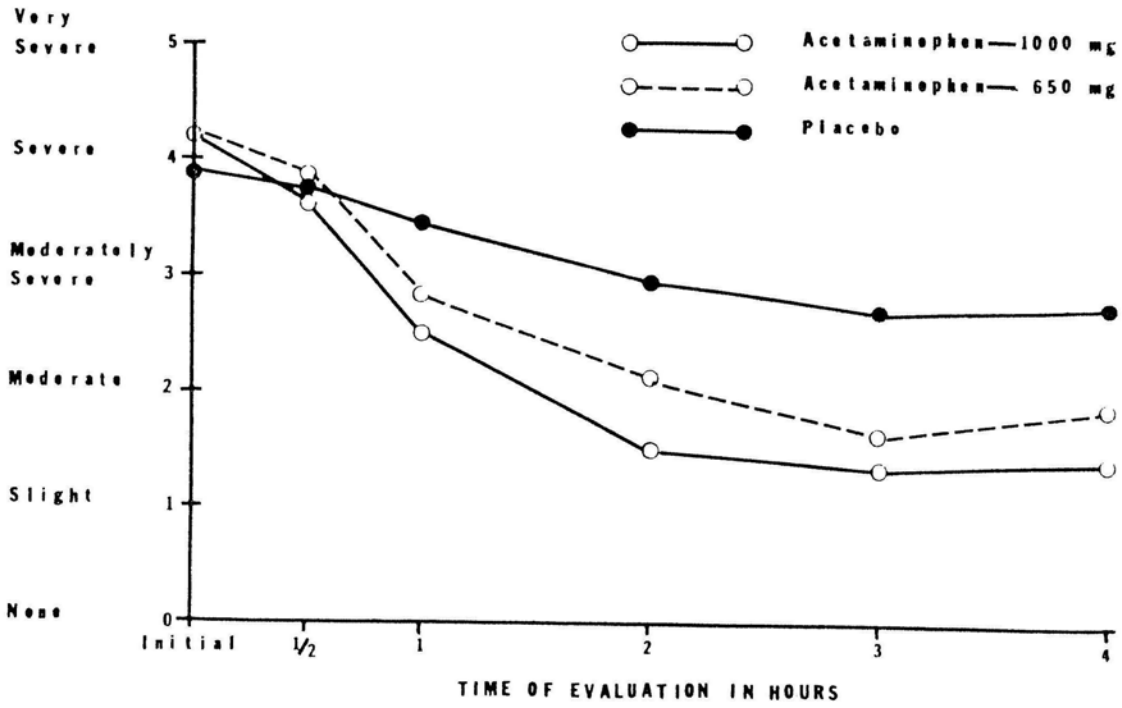

Figure 3-3. Pain Severity at Each Time Interval With Acetaminophen 1000 mg, Acetaminophen 650 mg, and Placebo

A summary of pain relief over time is presented in Figure 3-4. Acetaminophen 1000 mg provided significantly ($p<0.01$) greater pain relief compared to acetaminophen 650 mg and both were statistically significantly ($p<0.01$) superior to placebo.

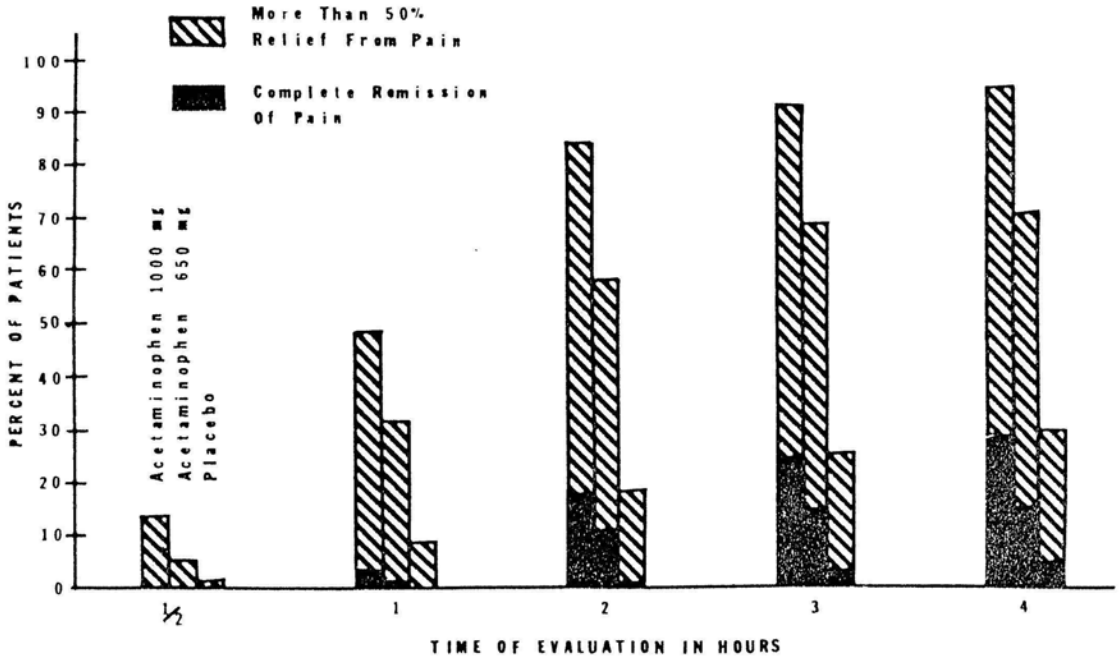

Figure 3-4. Pain Relief at Each Time Interval With Acetaminophen 1000 mg, Acetaminophen 650 mg, and Placebo

Significantly ($p<0.01$) more subjects required supplemental analgesic medication with placebo (33%) compared to either acetaminophen 1000 mg (6%) or acetaminophen 650 mg (10%). Global evaluations by the investigator are presented in Table 3-8. Acetaminophen 1000 mg was statistically significantly superior ($p<0.01$) to acetaminophen 650 mg and to placebo. Excellent or good results were achieved by 82% of subjects treated with acetaminophen 1000 mg, 58% of subjects treated with acetaminophen 650 mg, and 18% of subjects treated with placebo.

Table 3-8. Summary of Ratings for Global Evaluation

Evaluation	Acetaminophen 1000 mg N=87	Acetaminophen 650 mg N=88	Placebo N=88
Excellent	31	21	5
Good	40	30	11
Fair	12	17	12
Poor	2	10	24
No effect	2	10	36

3.7.1.6 Other McNeil Studies

3.7.1.6.1 McNeil Study 80-223

One randomized, double-blind, placebo-controlled, single-dose study conducted by McNeil [129] (80-223) also compared acetaminophen 1000 mg, acetaminophen 650 mg, and placebo in 152 subjects for the treatment of postoperative pain following dental surgery during the four-hour study period. Table 3-9 summarizes the demographic and baseline characteristics of the 152 subjects that entered the study. Overall, there were 56% females in each groups and the mean age was 28 years in the acetaminophen 1000 mg and 650 mg groups and 27 years in the placebo group. Baseline pain intensity was rated as moderate in 76 subjects and as severe in 47 subjects.

Table 3-9. Demographic and Baseline Characteristics – Study 80-223

Characteristic	Acetaminophen 1000 mg N=52	Acetaminophen 650 mg N=50	Placebo N=50
Mean Age, y	28	28	27
Mean Weight, lbs	159	150	151
Gender, n (%)			
Male	23 (44%)	22 (44%)	22 (44%)
Female	29 (56%)	28 (56%)	28 (56%)
Pain Intensity, n			
Moderate	29	26	21
Severe	10	17	20

Table 3-10 presents a summary of the analgesic measures by baseline pain intensity level. For subjects with moderate baseline pain intensity, acetaminophen 1000 mg was not significantly superior to acetaminophen 650 mg or placebo for any of the analgesic measures while acetaminophen 650 mg was significantly superior to placebo for total pain relief (TOTPAR), maximum pain relief (MAXPAR), sum of the pain intensity differences (SPID), number of hours in which initial pain was at least one-half relieved (HOURS), and global rating. For subjects with severe baseline pain intensity, acetaminophen 1000 mg was significantly superior to acetaminophen 650 mg for all analgesic measures and significantly superior to placebo for all analgesic measures except SPID ($p<0.05$, 1-tailed, as presented in the original report).

In addition, the percent of subjects with moderate baseline pain reporting a global evaluation of excellent or very good was 31% with acetaminophen 1000 mg, 43% with acetaminophen 650 mg, and 24% with placebo while the percent of subjects with severe baseline pain reporting a global evaluation of excellent or very good was 40% with acetaminophen 1000 mg, 6% with acetaminophen 650 mg, and 0% with placebo.

Table 3-10. Summary of Efficacy Measures – Study 80-223

Efficacy Measure[a] Baseline Pain	Acetaminophen 1000 mg	Acetaminophen 650 mg	Placebo
Mean TOTPAR			
Moderate	7.24	9.29[c]	5.45
Severe	6.55[b,c]	3.22	2.15
Mean MAXPAR			
Moderate	2.55	2.88[c]	2.05
Severe	2.60[b,c]	1.53	1.10
Mean SPID			
Moderate	2.90	3.79[c]	1.98
Severe	4.70[b]	2.47[c]	1.23
Mean MAXPID			
Moderate	1.10	1.23	0.81
Severe	1.80[b,c]	1.12[c]	0.55
Mean HOURS			
Moderate	1.91	2.65[c]	1.40
Severe	1.85[b,c]	0.79	0.33
Mean Global			
Moderate	2.62	3.04[c]	2.14
Severe	3.00[b,c]	2.00	1.40

a: Pain relief was recorded as none (0), a little (1), some (2), a lot (3) or complete (4); pain intensity was recorded as none (0), slight (1), moderate (2), or severe (3); pain half gone [HOURS] was recorded as initial pain at least one-half gone (1) or not (0); Global evaluations were recorded as poor (1), fair (2), good (3), very good (4), or excellent (5).
b: Significant ($p<0.05$, 1-tailed) vs acetaminophen 650 mg
c: Significant ($p<0.05$, 1-tailed) vs placebo

3.7.1.6.2 McNeil Study 80-214

One randomized, double-blind, placebo-controlled, single-dose study conducted by McNeil [130] (80-214) also compared acetaminophen 1000 mg, acetaminophen 650 mg, and placebo in 120 subjects for the treatment of postoperative pain following dental surgery during the six-hour study period. Table 3-11 summarizes the demographic and baseline characteristics of the 120 subjects that entered the study. Overall, there were 55%, 60%, and 64% females in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo

groups, respectively. The mean age was 22.34 y, 22.65 y, and 22.26 y in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively. Baseline pain intensity was rated as moderate in 51 subjects and as severe in 69 subjects.

Table 3-11. Demographic and Baseline Characteristics – Study 80-214

Characteristic	Acetaminophen 1000 mg N=38	Acetaminophen 650 mg N=40	Placebo N=42
Mean Age, y	22.34	22.65	22.26
Mean Weight, lbs	145.74	141.70	141.71
Gender, n (%)			
Male	17 (45%)	16 (40%)	15 (36%)
Female	21 (55%)	24 (60%)	27 (64%)
Pain Intensity, n			
Moderate	19	18	14
Severe	19	22	28

Table 3-12 presents a summary of the analgesic measures by baseline pain intensity level. For subjects with moderate baseline pain intensity, both acetaminophen 1000 mg and acetaminophen 650 mg were significantly superior to placebo for TOTPAR, MAXPAR, SPID, maximum pain intensity difference (MAXPID), HOURS, and global. For subjects with severe baseline pain intensity, acetaminophen 1000 mg was significantly superior to placebo for TOTPAR, MAXPAR, SPID, MAXPID, and HOURS while acetaminophen 650 mg was significantly superior to placebo for MAXPID. For subjects with severe baseline pain intensity, acetaminophen 1000 mg was significantly superior to acetaminophen 650 mg for HOURS ($p<0.05$, 1-tailed, as presented in the original report). No significant difference was observed among treatments for the percent of subjects remedicating.

Table 3-12. Summary of Efficacy Measures – Study 80-214

Efficacy Measure[a] Baseline Pain	Acetaminophen 1000 mg	Acetaminophen 650 mg	Placebo
Mean TOTPAR			
Moderate	11.26[c]	12.22[c]	4.14
Severe	6.63[c]	4.59	3.71
Mean MAXPAR			
Moderate	2.68[c]	2.94[c]	1.29
Severe	2.05[c]	1.50	1.14
Mean SPID			
Moderate	4.16[c]	4.61[c]	-0.07
Severe	4.63[c]	3.68	2.46
Mean MAXPID			
Moderate	1.16[c]	1.28[c]	0.21
Severe	1.37[c]	1.05[c]	0.68
Mean HOURS			
Moderate	3.37[c]	3.94[c]	1.21
Severe	2.21[b,c]	0.55	0.82
Mean Global			
Moderate	3.00[c]	3.00[c]	4.43
Severe	3.74	4.05	4.25
% remedicating			
Moderate	42.11	38.89	64.29
Severe	63.16	77.27	71.43

a: Pain relief was recorded as none (0), a little (1), some (2), a lot (3) or complete (4); pain intensity was recorded as none (0), slight (1), moderate (2), or severe (3); pain half gone [HOURS] was recorded as initial pain at least one-half gone (1) or not (0); Global evaluations were recorded as poor (1), fair (2), good (3), very good (4), or excellent (5).
b: Significant ($p<0.05$, 1-tailed) vs acetaminophen 650 mg
c: Significant ($p<0.05$, 1-tailed) vs placebo

3.7.1.6.3 McNeil Study 82-224

One randomized, double-blind, placebo-controlled, single-dose study conducted by McNeil [131] (Study 82-224) compared acetaminophen 1000 mg, acetaminophen 650 mg, and placebo in 54 subjects for the treatment of postoperative pain following oral surgery during the six-hour study period. There were 15, 19, and 20 subjects randomized to acetaminophen 1000 mg, acetaminophen 650 mg, and placebo, respectively. The mean age was 28.5 years, 28.4 years, and 28.2 years in the acetaminophen 1000 mg, acetaminophen 650 mg, and placebo groups, respectively and ranged from 18 to 52 years.

Overall, there were 19 males and 35 females and 39 subjects had moderate baseline pain while 15 subjects had severe baseline pain with the baseline pain intensity prior to treatment being similar across the three groups. Both acetaminophen 1000 mg and acetaminophen 650 mg were significantly ($p<0.05$, 1-tailed) superior to placebo for the sum of the pain relief scores (TOTPAR) and for peak pain relief while acetaminophen 1000 mg was significantly ($p<0.05$, 1-tailed) superior to placebo for peak pain intensity differences from baseline. No statistically significant differences were observed between acetaminophen 1000 mg and 650 mg for any of the analgesic parameters. The goal of this study was to see if the careful selection of subjects would permit the use of a smaller sample size without reducing assay sensitivity.

3.7.1.6.4 McNeil Study 80-210

One double-blind, placebo-controlled study conducted by McNeil [132] (Study 80-210) compared acetaminophen 1000 mg, acetaminophen 650 mg, and placebo in 112 subjects for the treatment of moderate to very severe pain following an episiotomy. The results presented here are from an interim analysis that recommended the study be discontinued. Of the 112 subjects, 40 subjects received acetaminophen 1000 mg, 37 subjects received acetaminophen 650 mg, and 35 subjects received placebo. Overall, 33 subjects reported moderate baseline pain, 66 subjects reported severe baseline pain, and 13 subjects reported very severe baseline pain. No significant differences existed among the three treatments for any variable except global rating.

3.7.1.7 Other Published Studies

Yuan et al conducted a single-dose, double-blind, randomized, placebo-controlled induced pain (cold-pressor test) study comparing acetaminophen 325 mg, 650 mg and 1000 mg [128] in 18 subjects. Dose-related analgesic activity was reported; there was a statistically significant main effect of dose, ie, pain and bothersomeness ratings decreased with increasing drug dose. However, in pair-wise comparisons, only the 1000 mg dose was statistically significantly superior to placebo.

3.7.2 Individual Clinical Studies Show That Acetaminophen 1000 mg is a Significantly More Effective Dose Than 500 mg

3.7.2.1 Pain

McNeil has conducted a single-dose, randomized, double-blind, placebo-controlled dental pain study that compared acetaminophen 1000 mg, acetaminophen 500 mg, and placebo

in 453 subjects with moderate to severe pain following dental surgery [13]. For the primary efficacy endpoint, Total Pain Relief over four hours, acetaminophen 1000 mg was significantly better than acetaminophen 500 mg ($p<0.0001$); this difference between 1000 mg and 500 mg translated to an approximate 42% greater pain relief. Figure 3-5 presents the time-action curve for pain relief. Acetaminophen 500 mg was significantly superior to placebo through four hours after dosing but not at Hours 5 and 6. By comparison, acetaminophen 1000 mg was significantly better than placebo for pain relief through Hour 6, the end of the observation period; at each observation time acetaminophen 1000 mg was also significantly better than acetaminophen 500 mg.

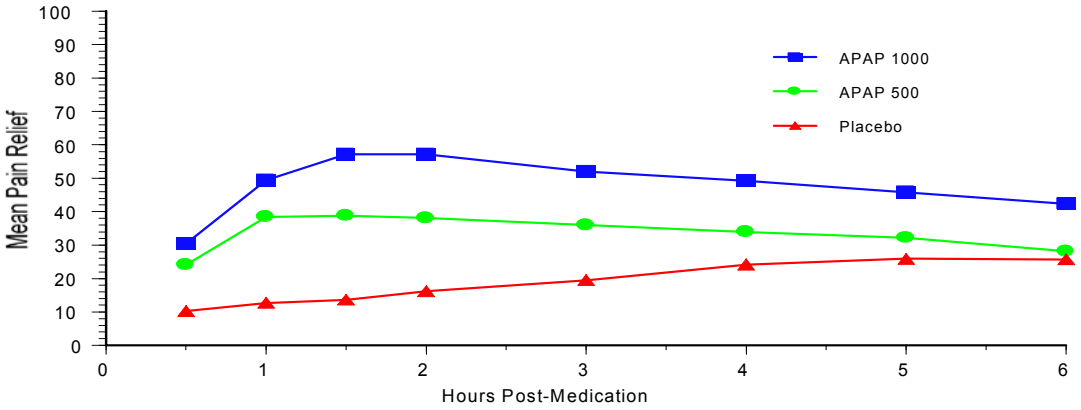

Figure 3-5. Mean Pain Relief from Baseline – Study 02-156

Acetaminophen 1000 mg was significantly superior to both acetaminophen 500 mg and to placebo for all other secondary endpoints including the sum of the pain intensity difference from baseline over four hours, the sum of the pain intensity difference and pain relief over four hours, pain intensity difference from baseline and pain relief from baseline at each assessed time point, time to rescue rates, and subjects overall impression of study medication. Acetaminophen 500 mg was significantly superior to placebo for all secondary endpoints except the pain intensity difference from baseline and pain relief from baseline at each assessed time point. For these, acetaminophen 500 mg was significantly superior to placebo at all time points except five and six hours postdose for pain relief and six hours postdose for pain intensity difference. The magnitude of this benefit of acetaminophen 1000 mg represents a robust and clinically important benefit.

Three other controlled clinical dental pain studies also demonstrate the superior efficacy of acetaminophen 1000 mg compared to acetaminophen 500 mg [14-16].

Quiding et al conducted a double-blind, randomized, dental pain study comparing codeine 60 mg, acetaminophen 500 mg and acetaminophen 1000 mg, for two doses for up to 10 hours [14]. One hundred eight subjects were included in the analysis. After a single dose, a 55% reduction in pain was reported for acetaminophen 1000 mg compared with a 30% reduction for acetaminophen 500 mg; this difference was statistically significant. After the second dose, a 67% reduction in pain was reported for acetaminophen 1000 mg compared with a 39% reduction for acetaminophen 500 mg; this difference was also statistically significant.

Nystrom et al conducted a double-blind, randomized, dental pain study comparing a single dose of diflunisal 500 mg to two doses of acetaminophen 500 mg and 1000 mg [15]. One hundred thirty-two subjects were included in the analysis. After a single dose, a 36% reduction in pain was reported for acetaminophen 1000 mg compared with a 10% reduction for acetaminophen 500 mg; this difference was statistically significant. After the second dose, a 46% reduction in pain was reported for acetaminophen 1000 mg compared with a 15% reduction for acetaminophen 500 mg; this difference was also statistically significant. The mean duration of pain relief was 4.6 hours for 1000 mg and 3.3 hours for acetaminophen 500 mg; this difference was statistically significant.

Seymour et al conducted a double-blind, randomized, placebo-controlled dental pain study comparing ketoprofen 12.5 mg and 25 mg, and acetaminophen 500 mg and 1000 mg [16]. Two hundred subjects were included in the analysis, with 40 subjects in each of the acetaminophen groups. Both acetaminophen doses provided statistically significantly superior pain relief (AUC 0-360) compared to placebo. Acetaminophen 1000 mg was numerically better than the 500 mg dose, however this difference did not reach statistical significance.

One study in postorthopedic surgery pain [123] also demonstrated statistically significantly superior efficacy of acetaminophen 1000 mg compared to acetaminophen 500 mg for various analgesic measures. In another study of experimentally-induced painful conditions [124], acetaminophen 1000 mg provided statistically significantly superior efficacy compared with placebo, but acetaminophen 500 mg did not.

Other clinical studies have failed to demonstrate the superior efficacy of acetaminophen 1000 mg compared to acetaminophen 500 mg in the dental pain model [29, 65, 67, 125] and in experimentally-induced painful conditions [126].

3.7.2.2 Fever

A randomized, double-blind placebo-controlled study in febrile respiratory infection found quantitatively better fever reduction among subjects treated with acetaminophen 1000 mg, compared to those who were treated with acetaminophen 500 mg, as shown in Figure 3-6, excerpted from Bachert et al [112].

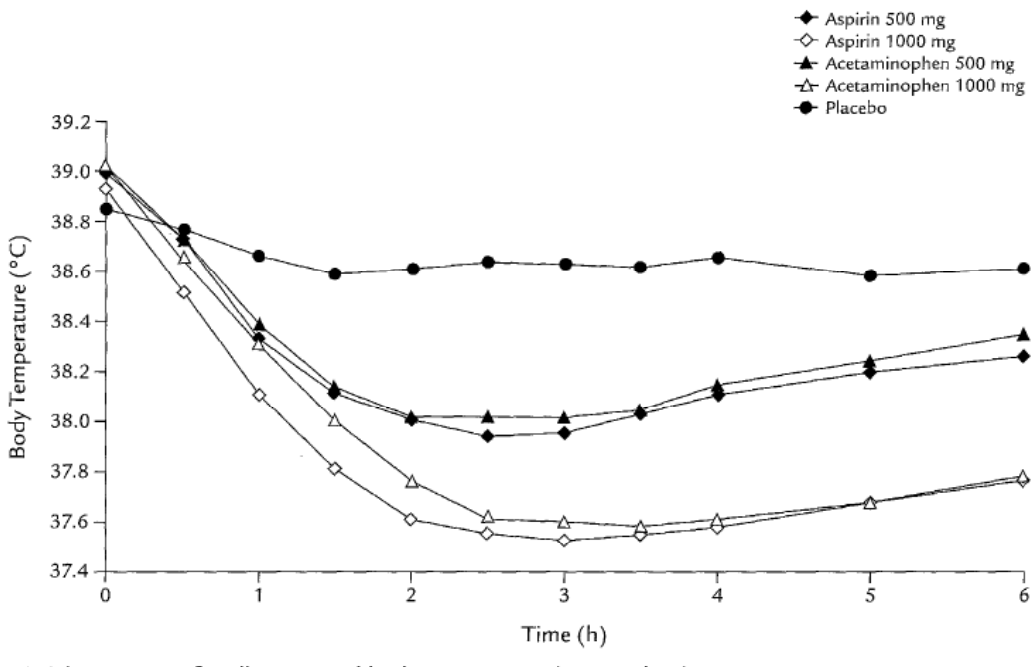

Figure 3-6. Antipyretic Time Course of Single Doses of Acetaminophen and Aspirin 500 mg and 1000 mg

3.7.3 Meta-Analyses Show that Acetaminophen 975/1000 mg is a Significantly More Effective Dose Than 600/650 mg

3.7.3.1 Published Meta-Analyses

Several meta-analyses have been published that compare the relative efficacy of various acetaminophen doses (600/650 mg and 1000 mg). Since the original meta-analysis was published in 2002 by McQuay et al [133], additional published studies of single-dose oral acetaminophen in postoperative pain have become available. Updates of the original meta-analysis were performed in 2004 [134] and 2008 [135] by McQuay and colleagues. These analyses quantified efficacy using the concept of "number-needed-to-treat (NNT)" although this calculation is not a traditional endpoint in analgesic studies. The NNT was defined as the number of subjects required to receive a particular acetaminophen dose in order for one subject to achieve at least 50% pain relief at that dose, compared with placebo, over a four- to six-hour treatment period. The more effective the acetaminophen dose, the lower the NNT.

The most current meta-analysis by Toms et al [135] updated the searches performed by McQuay [133] through July 2008 and included reports of randomized, double-blind, placebo-controlled clinical trials of adults with postoperative pain of moderate-to-severe intensity evaluated over a four- to six-hour treatment period. As shown in Table 3-13, The NNT for acetaminophen 975/1000 mg versus placebo was 3.6 (95% CI, 3.2 - 4.1) and the NNT for acetaminophen 600/650 mg versus placebo was 4.6 (95% CI, 3.9 - 5.5). Acetaminophen 975/1000 mg had a lower NNT compared to acetaminophen 600/650 mg, which indicated that it was more effective. However, no statistically significant difference was observed between the two acetaminophen doses.

Table 3-13. Meta-Analysis Results for Single-Dose Efficacy of Acetaminophen 975/1000 mg and 600/650 mg Compared with Placebo [135]

	At least 50% pain relief with		
	Acetaminophen	Placebo	
	N	N	NNT
Dose (mg)	(%)	(%)	(95% CI)
975/1000	876/1903	241/1329	3.6 (3.2 - 4.1)
(28 studies)	(46)	(18)	
600/650	358/954	145/932	4.6 (3.9 – 5.5)
(19 studies)	(38)	(16)	

3.7.3.2 McNeil and J&J PRD Meta-Analysis

A meta-analysis was conducted by McNeil of the raw data provided in the meta-analysis by Toms et al [135] combined with data from 37 unpublished studies conducted by McNeil and Johnson & Johnson Pharmaceuticals Research and Development (J&J PRD) that had the same inclusion criteria as that used by Toms et al. This meta-analysis investigated the proportion of patients achieving at least 50% of the maximum total pain relief (TOTPAR) score. Mean TOTPAR was converted to the proportion of patients achieving at least 50% of the maximum TOTPAR score using methods described by Moore and colleagues [136]. For the meta-analysis, the results of the four studies included in the NDA (Hopkinson, Bare, Posatko, Wallach) were used as presented in Hopkinson [127] as this publication gave more detailed pain relief data than any of the individual reports. Hopkinson presented a combined analysis of three of the four studies and did not include the results from Wallach in which no difference from placebo was seen for either 650 mg or 1000 mg of acetaminophen due to a high placebo response. These three studies are considered to be one study in the analyses that follow.

Classical and Bayesian random-effects models of log-odds ratios (log-ORs) for all direct comparisons (975/1000 mg vs placebo, 600/650 mg vs placebo, and 975/1000 mg vs 600/650 mg) were conducted, using an inverse-variance-weighting method. Results were inspected for heterogeneity, using I^2 and Cochran's Q, and sensitivity analyses investigating the effect of outliers were conducted. Raw sample-size weighted mean proportions of 50% TOTPAR were then calculated for the placebo group. This proportion, in combination with the estimated odds-ratios (OR) and 95% OR confidence intervals, was used to calculate direct-comparison NNTs, with 95% confidence intervals.

Table 3-14 presents the results for the meta-analysis of acetaminophen 975/1000 mg, acetaminophen 600/650 mg, and placebo. Treatment for moderate and severe pain with acetaminophen 975/1000 mg led to a higher proportion of patients achieving 50% maximum TOTPAR than treatment with acetaminophen 600/650 mg; the indirect comparison was statistically significant (p=0.01) and the direct comparison of 600/650 mg to 975/1000 mg was not significant, though the odds ratio (OR) estimates were similar for the indirect (OR = 1.55) and the direct (OR = 1.32) comparisons.

Table 3-14. Meta-Analysis Results for the Proportion of Patients Experiencing At Least 50% Pain Relief After Postoperative Pain Treatment With Acetaminophen 975/1000 mg, Acetaminophen 600/650 mg, and Placebo

Treatment Arms	No. of Studies (No. Patients)	Odds Ratio[a] [95% CI]	NNT [95% CI]	p-value
Direct Comparisons				
975/1000 vs placebo	58 (5806)	5.24 [4.21, 6.51][b]	2.82 [2.45, 3.33]	<0.001
600/650 vs placebo	34 (3011)	3.38 [2.62, 4.37][b]	4.07 [3.24, 5.40]	<0.001
975/1000 vs 600/650	5 (466)	1.32 [0.80, 2.20][c]	22.39 [-32.66, 6.97]	0.28
Indirect Comparison				
975/1000 vs 600/650		1.55 [1.11, 2.17]	9.17 [5.24, 39.57]	0.010

a: An odds ratio >1 indicates a higher proportion of patients achieving 50% of the maximum TOTPAR for the first treatment relative to the second.
b: Denotes highly significant heterogeneity (p<0.001)
c: I^2 = 36%

The direct comparison of acetaminophen 975/1000 mg vs placebo and acetaminophen 600/650 mg vs placebo showed significant superiority of all doses of acetaminophen compared with placebo (p<0.001).

Heterogeneity testing showed a moderate amount of between-study inconsistency for direct comparisons of each dose to placebo with I^2 of 44% to 53%. This heterogeneity was statistically significant (p<0.05). I^2 was 36% for the direct comparison of 600/650 mg to 975/1000 mg; this was not statistically significant. An inspection of individual effects did not find that any given study was a noticeably strong outlier; rather, the between-study variation seemed to be relatively evenly distributed. For all comparisons against placebo, the heterogeneity reflects variability in effects, but directionally all studies show numerical superiority to placebo.

Forest plots for each of the comparisons are shown in Figure 3-7 through Figure 3-11.

In summary, these meta-analyses provide evidence that treatment with acetaminophen 975/1000 mg results in a greater proportion of patients achieving 50% maximum TOTPAR relative to treatment with acetaminophen 600/650 mg with a point estimate of the odds ratio from 1.32 to 1.55.

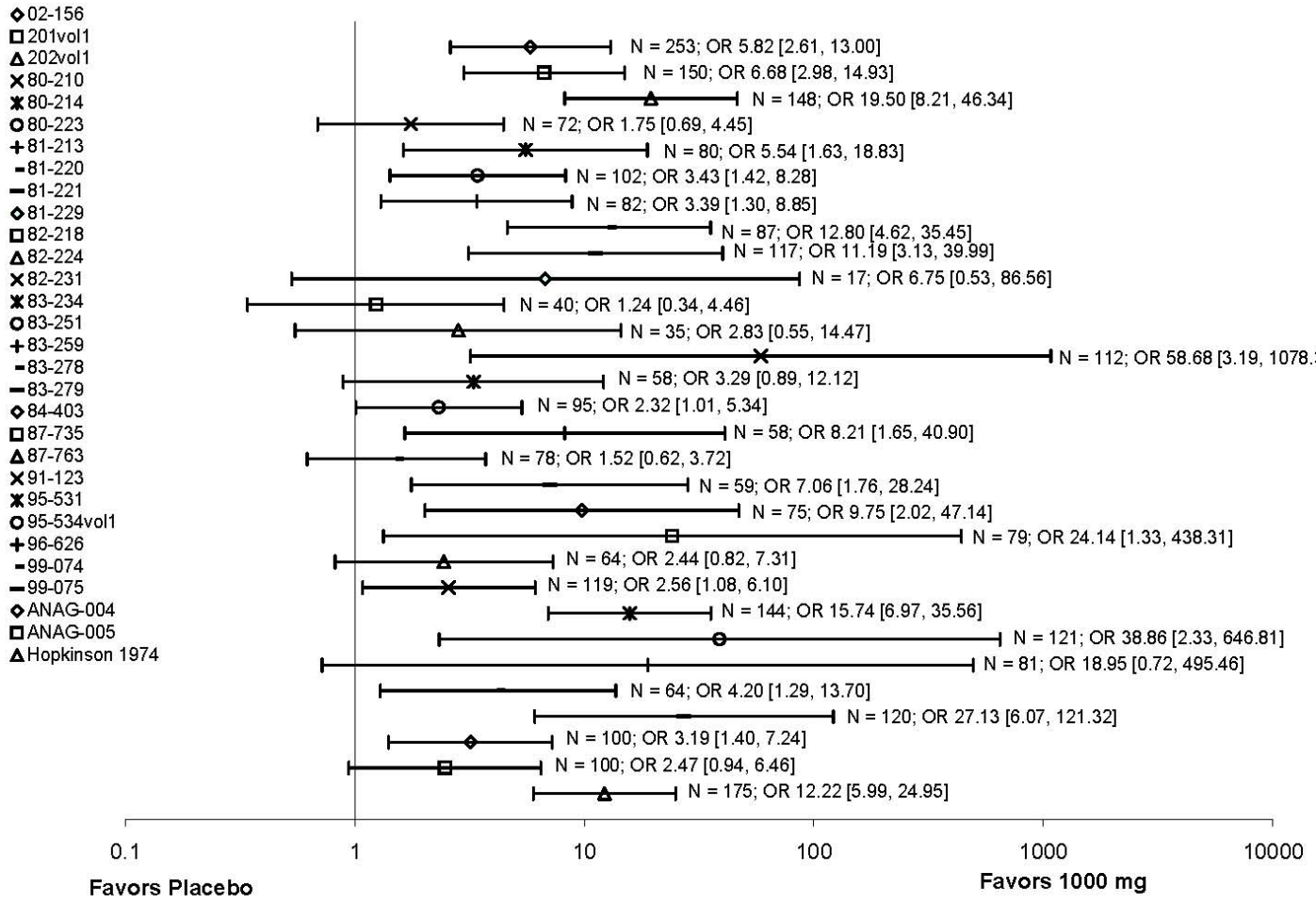

Figure 3-7. Acetaminophen 1000 mg vs Placebo, Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, mean odds ratio [95% confidence interval]

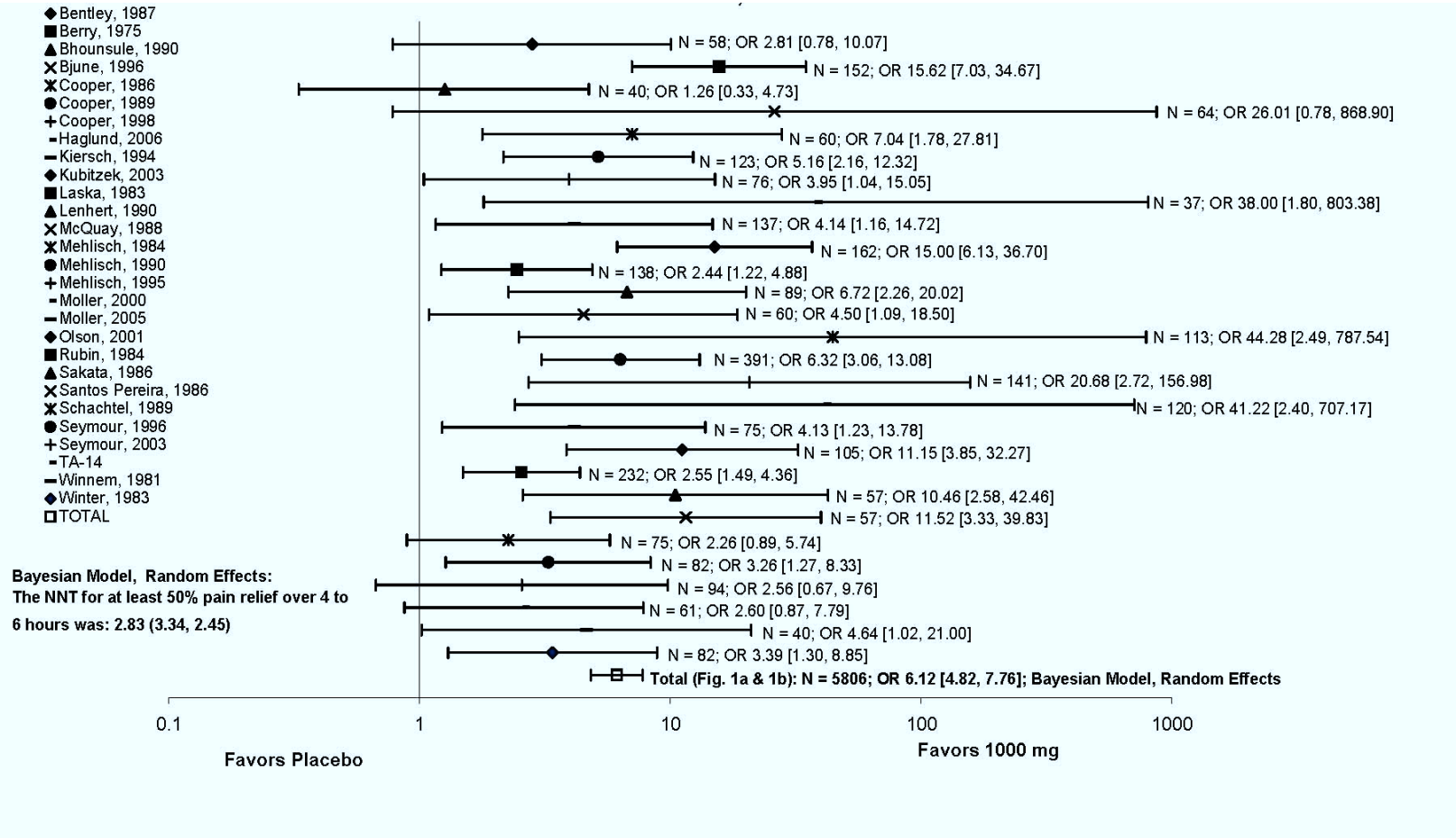

Figure 3-7. **Acetaminophen 1000 mg vs Placebo, Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, mean odds ratio [95% confidence interval]**

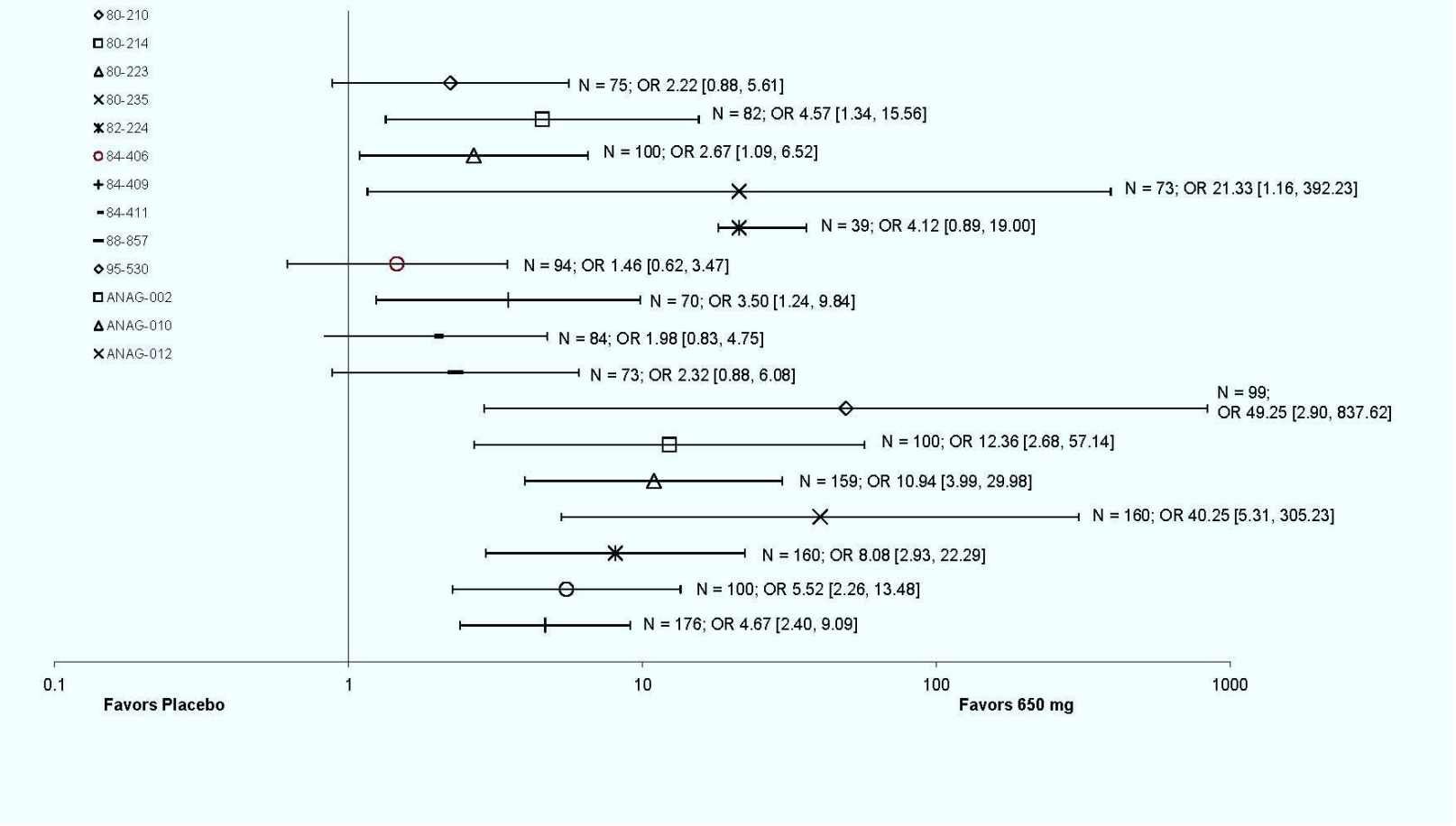

Figure 3-8. Acetaminophen 650 mg vs Placebo, Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, mean odds ratio [95% confidence interval]

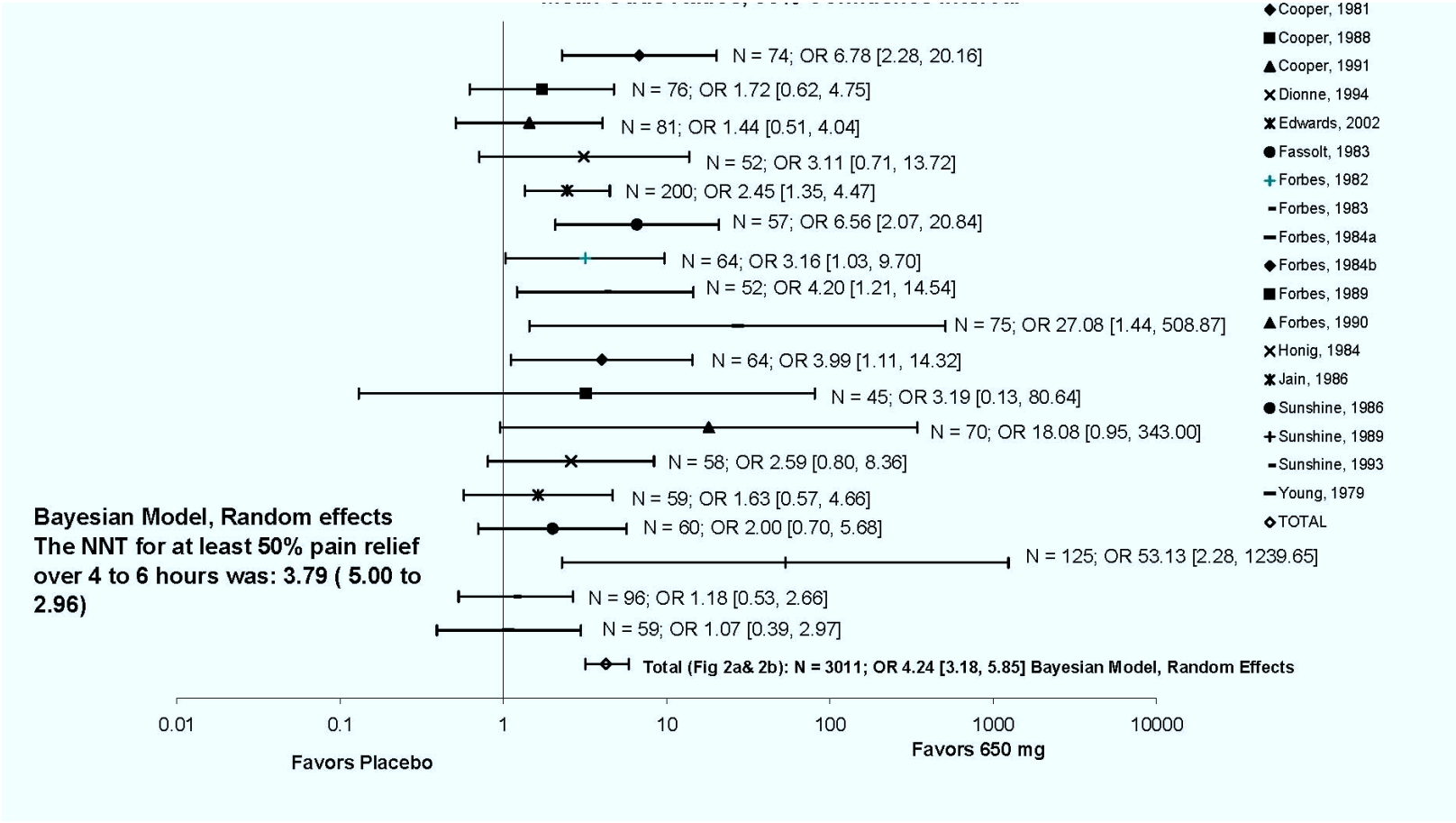

Figure 3-8. Acetaminophen 650 mg vs Placebo, Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, mean odds ratio [95% confidence interval]

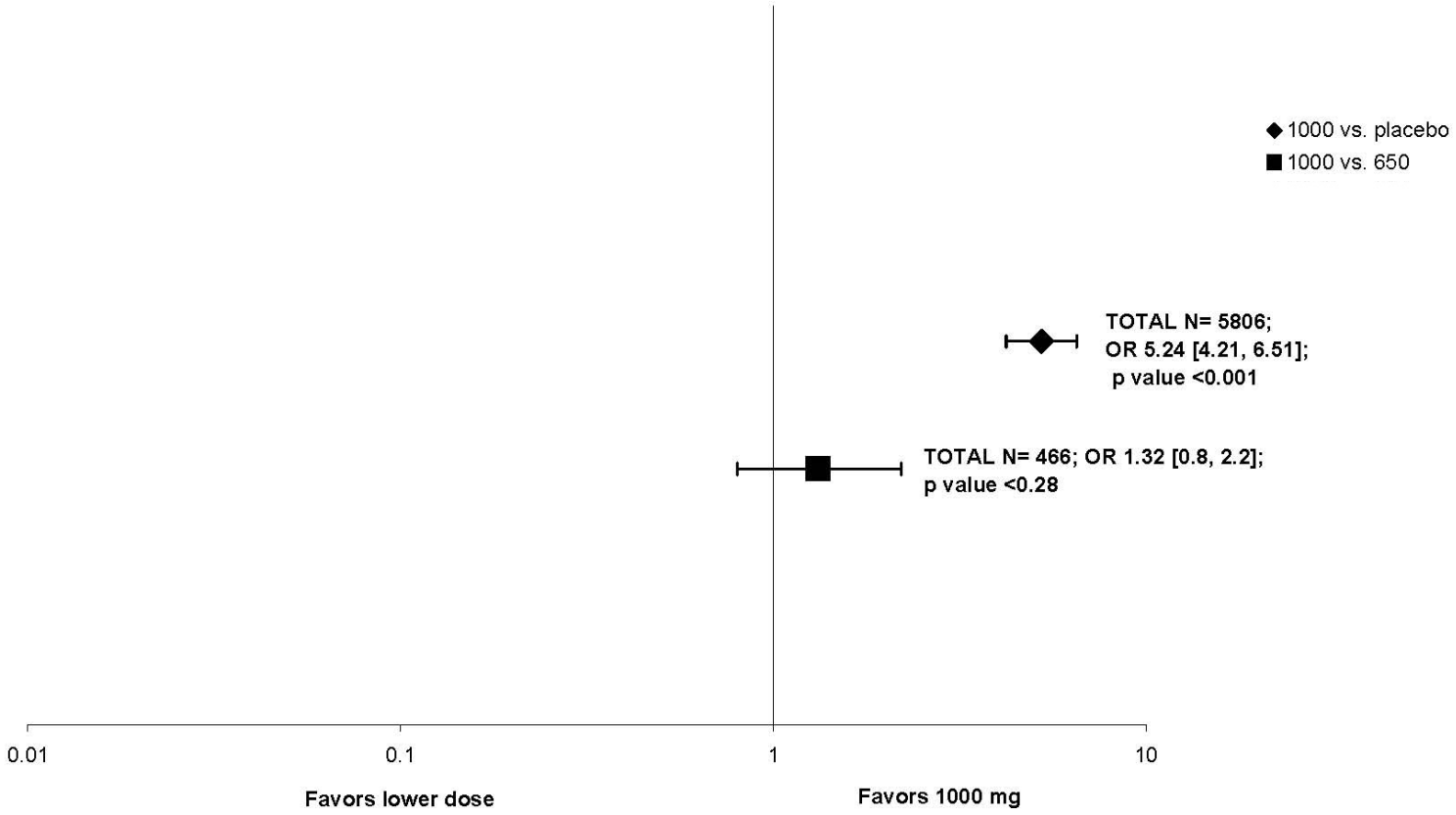

Figure 3-9. Comparisons of Acetaminophen 1000 mg to Acetaminophen 650 mg, Odds Ratios of Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, direct classical MA Model Random Effects [95% confidence interval]

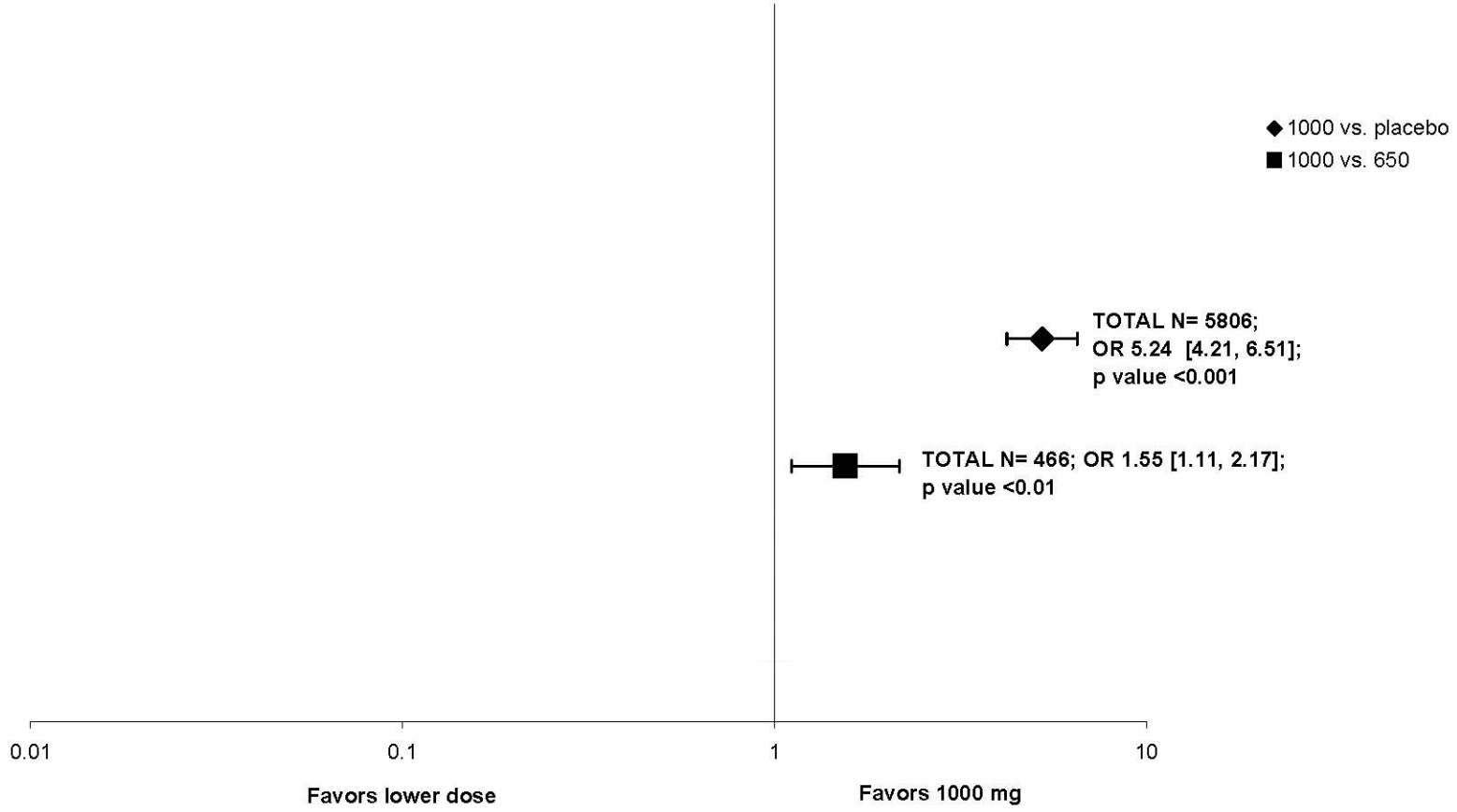

Figure 3-10. Comparisons of Acetaminophen 1000 mg to Acetaminophen 650 mg, Odds Ratios of Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, indirect classical Model Random Effects [95% confidence interval]

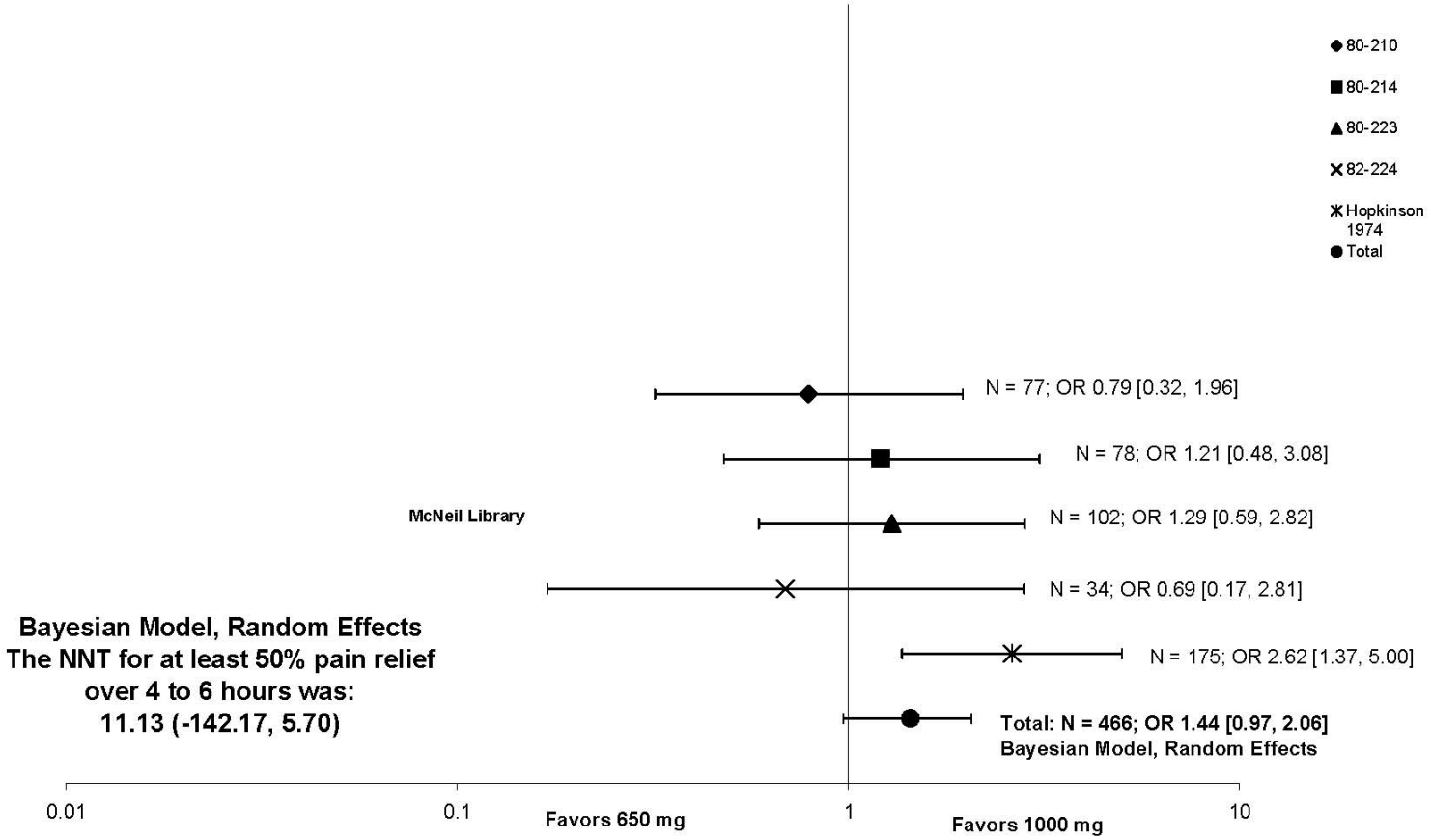

Figure 3-11. Acetaminophen 1000 mg vs 650 mg, Odds Ratios of Subjects with at least 50% of maximum TOTPAR in 4-6 hour studies, Mean Odds Ratios [95% confidence interval]

3.7.4 Acetaminophen Concentration–Response Model Indicates 1000-mg Dose Exceeds the EC50 Concentration Predicted for Dental Pain

Based on pharmacokinetic-pharmacodynamic (PK-PD) modeling, acetaminophen 1000 mg yields peak plasma concentrations that consistently meet or exceed the EC_{50} (concentration in the effect compartment that elicits 50% of the maximum drug response) [137, 138]. These PK-PD results are consistent with the meta-analyses of acetaminophen [133-136] and with individual placebo-controlled studies [13-16, 112, 123-124, 127-128] that report numerically or statistically significantly greater efficacy of acetaminophen 1000 mg, compared with lower doses.

Acetaminophen concentration-response relationship using pain relief data from dental surgery has been explored. One population PK-PD model was developed using data from 114 subjects in dental pain study, who received a single dose of acetaminophen 1000 mg (either caplet or effervescent solution) or placebo [137]. Another PK-PD model used data obtained from male patients who received two doses of acetaminophen 650 mg in a dental pain study coupled with data obtained in a separate a PK study [138]. Both models found that, similar to other orally administered analgesics, the initial analgesic effect of acetaminophen lags behind the increase in plasma concentration, so an effect compartment model was used to link the pharmacokinetic and pharmacodynamic data. Estimates of the pharmacodynamic parameters obtained for acetaminophen analgesia were very similar in both models: the EC_{50} was 15.2 µg/mL [141] and 16.55 µg/mL [138].

To further assess the relationship among the 650 mg and 1000 mg doses, corresponding plasma concentrations and the EC_{50}, McNeil examined single-dose pharmacokinetic data available from several published studies [139-150]. As shown in Figure 3-12 across these studies, the mean acetaminophen C_{MAX} following a 1000 mg dose consistently approaches or exceeds the two EC_{50} estimates noted above (ie, 15.2 µg/mL and 16.55 µ/mL), whereas the 650 mg dose did not. These data further support that 1000 mg is the most appropriate single analgesic dose, and provides a clinical pharmacologic rational to maintain the current maximum allowable single dose, 1000 mg. A limitation of this cross-study assessment is that C_{MAX} is not the only drug exposure metric that relates to response through EC_{50}, and that total drug exposure is likely related.

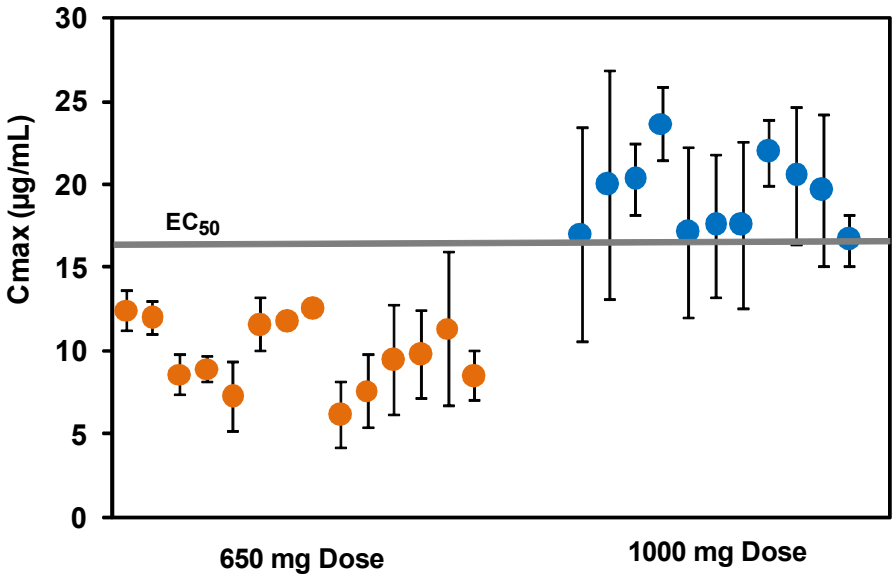

Figure 3-12. Acetaminophen CMAX Means for 650 mg and 1000 mg Doses Show that 1000 mg Consistently Attains Plasma Concentrations Having 50% Maximum Effect

3.7.5 Summary

Although the number of clinical trials that have directly compared acetaminophen 1000 mg to acetaminophen 650 mg is relatively small, the majority demonstrate additional effectiveness with the higher dose. In addition, meta-analyses show that a greater number of subjects achieve pain relief with acetaminophen 1000 mg compared to acetaminophen 650 mg. Furthermore, pharmacokinetic-pharmacodynamic (PK-PD) modeling shows that acetaminophen 1000 mg consistently exceeds or approaches the plasma concentration needed for 50% of maximum analgesic effect (EC_{50}), whereas acetaminophen 650 mg does not. Taken together, these data clearly support that acetaminophen 1000 mg provides more analgesia than acetaminophen 650 mg.

3.8 Acetaminophen Dosing Interval

Because pain and fever may last longer than the effective duration of any OTC analgesic/antipyretic, the dosing interval can be as highly relevant to an individual as the dose taken at each occasion. Both pharmacokinetic and clinical data support the continuing appropriateness of the four- to six-hour dosing interval for acetaminophen.

Multiple pain studies reviewed above have demonstrated that 1000 mg provides significantly greater analgesic efficacy than either 650 mg or 500 mg. The duration of analgesic action of acetaminophen 1000 mg involving subjects with moderate to severe pain levels is approximately 4 to 6 hours, while the duration for acetaminophen 650 mg is approximately 4 hours. Operationally, this is consistent with the dosing interval for acetaminophen.

3.8.1 Efficacy of Acetaminophen 4000 mg Per Day for Multiple Days for Recurrent Pain

Adult OTC acetaminophen product labeling includes the following statement concerning duration of use: Stop use and ask a doctor if pain gets worse or lasts for more than ten days, if fever gets worse or lasts for more than three days, or if sore throat persists for more than two days. Clinical trials studying acetaminophen use for pain can be divided into those with a duration of less than ten days or greater than ten days. Safety and efficacy data from studies of longer duration (greater than ten days) are available to support the use of acetaminophen for prolonged periods as directed by a health care professional.

Multiple doses of acetaminophen 1000 mg taken for three to ten days have shown superior efficacy compared to placebo in a variety of models including post oral surgery pain [61, 67,79], arthritis pain [151; 153], painful conditions [157, 158], and dysmenorrhea [114]. Acetaminophen was well tolerated and no serious adverse events were reported in any of the studies.

The safety and efficacy of acetaminophen when compared to placebo or NSAIDs for the treatment of pain for extended time periods has been demonstrated in ten osteoarthritis trials involving approximately 1200 patients treated with acetaminophen [113-122]. These studies show that acetaminophen, when taken at the recommended daily dose of up to 4000 mg per day, demonstrated efficacy and an acceptable safety profile. The number of subjects and duration of acetaminophen therapy (25 subjects for three weeks [113], 99 subjects for four weeks [114], 61 subjects for four weeks [115], 52 subjects for eight weeks [116], 94 subjects for six weeks [117]), seven subjects for two weeks [118], 331 subjects for six weeks [119], 160 subjects for 12 weeks [120], 50 subjects for six months and 229 subjects for 12 months [121], and 136 subjects for four weeks [122] support the safe use of acetaminophen for extended periods of time. Results demonstrated that acetaminophen

was superior to placebo and comparable to NSAIDs (such as ibuprofen, celecoxib, and naproxen) regardless of the number of participants or duration of therapy.

Of these ten studies, one randomized, double-blind, placebo-controlled study [120] (Study 00-103) evaluated acetaminophen 3900 mg/day, acetaminophen 1950 mg/day, and placebo in the treatment in 483 subjects with osteoarthritis of the hip or knee. Overall, 160 subjects received acetaminophen 3900 mg/day, 158 subjects received acetaminophen 1950 mg/day, and 165 subjects received placebo. The mean age of the study population was 62.2 years and 67% were female.

There were three primary endpoints: the average change from baseline for all visits through final on-therapy visit for WOMAC pain subscale score, the average change from baseline through final on-therapy visit for WOMAC physical function subscale score, and the average subject's global assessment of response to therapy through final on-therapy visit. The average change from baseline across all visits through the final on-therapy visit for the WOMAC pain subscale score was significantly (p=0.0120) greater with acetaminophen 3900 mg/day than with placebo (-6.06) but was not significantly different with acetaminophen 1950 mg/day compared to placebo (-2.67). Table 3-15 presents a summary of the change from baseline in WOMAC pain subscale scores at each time point. Changes from baseline in the mean pain subscale score in the acetaminophen 3900 mg/day group were significantly greater than those in the placebo group at each time point after Week 2 (at Week 4 or final visit [p=0.0078], at Week 8 or final visit [p=0.0152], and at Week 12 or final visit [p=0.0087]. The changes from baseline in the mean pain subscale score in the acetaminophen 1950 mg/day group were similar to those in the placebo group at each time point and were not significantly different.

Table 3-15. Change From Baseline in WOMAC Pain Subscale Scores[a] at Each Time point– Study 00-103

Timepoint/Statistic	Acetaminophen 3900 mg/day N=160	Acetaminophen 1950 mg/day N=158	Placebo N=165
Week 2 or final on-therapy visit			
LS Mean Difference (SE)	-20.4 (1.693)	-18.2 (1.696)	-17.0 (1.665)
p-Value[b]	0.1395	0.6071	
Week 4 or final on-therapy visit			
LS Mean Difference (SE)	-25.3 (1.911)	-21.5 (1.913)	-18.3 (1.881)
p-Value[b]	0.0078	0.2206	
Week 8 or final on-therapy visit			
LS Mean Difference (SE)	-28.1 (2.055)	-23.5 (2.058)	-21.2 (2.023)
p-Value[b]	0.0152	0.4283	
Week 12 or final on-therapy visit			
LS Mean Difference (SE)	-30.3 (2.137)	-26.1 (2.140)	-22.6 (2.103)
p-Value[b]	0.0087	0.2436	

a: All WOMAC subscale scores were normalized to a scale of 0 to 100. Missing data were imputed by using last observation carried forward.
b: Comparison vs placebo.

The average change from baseline across all visits through the final on-therapy visit for the WOMAC physical function subscale score was significantly (p=0.0157) greater with acetaminophen 3900 mg/day than with placebo (-5.95) but was not significantly different with acetaminophen 1950 mg/day compared to placebo (-0.80). Table 3-16 presents a summary of the change from baseline in WOMAC pain subscale scores at each time point. Changes from baseline in the mean physical function subscale score in the acetaminophen 3900 mg/day group were significantly greater than those in the placebo group at each time point after Week 2 (at Week 4 or final visit [p=0.0147], at Week 8 or final visit [p=0.0161], and at Week 12 or final visit [p=0.0231]. The changes from baseline in the mean pain subscale score in the acetaminophen 1950 mg/day group were similar to those in the placebo group at each time point and were not significantly different.

Table 3-16. Change From Baseline in WOMAC Physical Function Subscale Scores[a] at Each Time Point – Study 00-103

Timepoint/Statistic	Acetaminophen 3900 mg/day N=160	Acetaminophen 1950 mg/day N=158	Placebo N=165
Week 2 or final on-therapy visit			
LS Mean Difference (SE)	-18.1 (1.670)	-14.7 (1.671)	-14.6 (1.645)
p-Value[b]	0.1262	0.9421	
Week 4 or final on-therapy visit			
LS Mean Difference (SE)	-23.8 (1.921)	-17.8 (1.922)	-17.4 (1.892)
p-Value[b]	0.0147	0.8764	
Week 8 or final on-therapy visit			
LS Mean Difference (SE)	-26.4 (2.097)	-20.3 (2.098)	-19.5 (2.065)
p-Value[b]	0.0161	0.7773	
Week 12 or final on-therapy visit			
LS Mean Difference (SE)	-28.1 (2.152)	-23.0 (2.153)	-21.4 (2.119)
p-Value[b]	0.0231	0.6058	

a: All WOMAC subscale scores were normalized to a scale of 0 to 100. Missing data were imputed by using last observation carried forward.
b: Comparison vs placebo.

The average subject's assessment of response to therapy through on-therapy visit was slightly higher than 2.0 in the acetaminophen 3900 mg/day and acetaminophen 1950 mg/day groups, indicating a fair response to therapy, whereas the mean score was lower than 2.0 in the placebo group. The mean score was significantly greater with acetaminophen 3900 mg/day (p=0.0153) and acetaminophen 1950 mg/day (p=0.0236) than with placebo. Table 3-17 presents the mean score for the subject's average assessment of response to therapy at each time point. The mean in the acetaminophen 3900 mg/day group were significantly greater than that in the placebo group at each time point after Week 2 (at Week 4 or final visit [p=0.0095], at Week 8 or final visit [p=0.0208], and at Week 12 or final visit [p=0.0111]. The mean for average subject's assessment of response in the acetaminophen 1950 mg/day group was also significantly greater than in the placebo group at Week 4 or final visit (p=0.0289) and at Week 8 or final visit (p=0.0243).

Table 3-17. Subject Assessment of Response to Therapy at Each Time Point – Study 00-103

Timepoint/Statistic[a]	Acetaminophen 3900 mg/day N=160	Acetaminophen 1950 mg/day N=158	Placebo N=165
Week 2 or final on-therapy visit			
LS Mean Difference (SE)	1.98 (0.096)	2.01 (0.096)	1.75 (0.094)
p-Value[b]	0.0744	0.0461	
Week 4 or final on-therapy visit			
LS Mean Difference (SE)	2.12 (0.096)	2.06 (0.096)	1.78 (0.095)
p-Value[b]	0.0095	0.0289	
Week 8 or final on-therapy visit			
LS Mean Difference (SE)	2.13 (0.100)	2.12 (0.101)	1.81 (0.099)
p-Value[b]	0.0208	0.0243	
Week 12 or final on-therapy visit			
LS Mean Difference (SE)	2.20 (0.105)	2.10 (0.105)	1.84 (0.103)
p-Value[b]	0.0111	0.0646	

a: Missing data were imputed by using last observation carried forward.
b: Comparison vs placebo.

3.9 Safety of Acetaminophen

A review of multiple-dose acetaminophen clinical studies indicates that at the current maximum single dose, 1000 mg, and the current maximum daily dosage, 4000 mg, acetaminophen is well tolerated and has a favorable safety profile.

3.9.1 Short-term Clinical Trials

Acetaminophen 1000 mg has been administered under controlled conditions for 2 to 10 days to treat a variety of conditions, including oral surgery pain [16, 61, 67, 79, 152], arthritis pain [153], fever [154], muscle aches and pains [155,156], dysmenorrhea [107], and other painful conditions [157,158]. These studies demonstrate that acetaminophen is well tolerated and not associated with serious adverse events.

3.9.2 Longer-term Clinical Trials

Acetaminophen's tolerability in longer-term use has been demonstrated in osteoarthritis trials similar to situations of physician supervised care involving approximately 1500 subjects treated with acetaminophen [113-122, 159, 160]. Daily acetaminophen dosages of up to 4000 mg per day were taken. The duration of use ranged from three weeks [113] to

twelve months [121] and, taken together, demonstrated no evidence of hepatotoxicity, hepatic dysfunction, or hepatic failure. These data support that, even at durations substantially exceeding the ten-day OTC maximum, acetaminophen up to 4000 mg per day is well tolerated.

3.10 Reference List

1. Sachs CJ. Oral analgesics for acute nonspecific pain. Am Fam Phys 2005;7195:913-918.
2. Arthritis Foundation. Atlanta (GA): Arthritis Foundation; 1999. Pain factsheet. Pain in America: highlights from a Gallup Survey on Pain; available at: http:www.arthritis.org/conditions/speakingofpain/factsheet.asp.
3. Carr D, Chao S, Polomano R, et al. Restricting dosage or availability of OTC analgesics: A model for analysis. APS Bulletin 2002:12(5).
4. BenDebba M, Torgerson WS, Long DM. Personality traits, pain duration and severity, functional impairment, and psychological distress in patients with persistent low back pain. Pain 1997;72:115-125.
5. Foley KM. Pain relief into practice: Rhetoric without reform. J Clin Oncol 1995 Sep;13:2149-2151.
6. Linton SJ. Overlooked and undertreated? The role of acute pain intensity in the development of chronic low back pain problems. Pain Forum 1997;6:145-147.
7. McCaffrey M, Pasero BR. Pain: Clinical Manual 1999. St Louis: Mosby.
8. Page GG. The medical necessity of adequate pain management. Pain Forum 1996;5:227-231.
9. Gureje O, Von Korff M, Simon GE, et al. Persistent pain and well-being: A World Health Organization study in primary care. JAMA 1998;280:147-151.
10. Snelling J. The effect of chronic pain on the family unit. J Adv Nurs 1994;19:543-551.
11. McNeil Consumer Healthcare Clinical Study Report for Protocol 11-202: A randomized, double-blind, double-dummy, placebo-controlled, parallel group study of acetaminophen 1000 mg and ibuprofen 400 mg in postoperative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, August 2004a (data on file).
12. McNeil Consumer Healthcare Clinical Study Report for Protocol 11-201: A randomized, double-blind, double-dummy, placebo-controlled, parallel group study of acetaminophen 1000 mg and ibuprofen 400 mg in postoperative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, August 2004b (data on file).
13. McNeil Consumer Healthcare Clinical Study Report for Protocol 02-156: A single-dose, double-blind, placebo-controlled study of the relative efficacy and safety of acetaminophen at doses of 500 mg and 1000 mg in postoperative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, February 2004a (data on file).
14. Quiding H, Oikarinen V, Sane J, et al. Analgesic efficacy after single and repeated doses of codeine and acetaminophen. J Clin Pharmacol 1984;24:27-34.
15. Nystrom E, Gustafsson I, Quiding H. The pain intensity at analgesic intake and the efficacy of diflunisal in single doses and effervescent acetaminophen in single and repeated doses. Pharmacotherapy 1988;8:201-209.
16. Seymour RA, Kelly PJ, Hawkesford JE. The efficacy of ketoprofen and paracetamol (acetaminophen) in postoperative pain after third molar surgery. Brit J Clin Pharmacol 1996;41:581-585.
17. Kubitzek F, Ziegler G, Gold MS, et al. Analgesic efficacy of low-dose diclofenac versus paracetamol and placebo in postoperative dental pain. J Orofac Pain 2003;17:237-244.

18. Olson NZ, Otero AM, Marrero I, et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. J Clin Pharm 2001;41:1238-1247.

19. Moller PL, Noerholt SE, Ganry HE, et al. Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: A single-dose, double-blind, randomized, placebo controlled study. J Clin Pharm 2000;40:370-378.

20. Sunshine A, Otero A, Olson NZ, et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg and placebo on postsurgical dental pain. Clin Pharmacol Ther 2000;67:145 (abstract).

21. Hersh EV, Levin LM, Cooper SA, et al. Ibuprofen liquigel for oral surgery pain. Clin Ther 2000;22:1306-1318.

22. McNeil Consumer Healthcare Clinical Study Report for Protocol 99-075: A randomized, double-blind, triple-dummy, placebo-controlled study evaluating the analgesic effect of using a single dose of acetaminophen 1000 mg, celecoxib 100 mg or ibuprofen 400 mg in postoperative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, December 2000 (data on file).

23. RW Johnson Pharmaceutical Research Institute Clinical Study Report for Protocol TRAMAP-ANAG-012: Evaluation of the efficacy and safety of tramadol/APAP in oral surgical pain. July 1999a (data on file).

24. RW Johnson Pharmaceutical Research Institute Clinical Study Report for Protocol TRAMAP-ANAG-010: Evaluation of the efficacy and safety of tramadol/APAP in oral surgical pain. July 1999 (data on file).

25. RW Johnson Pharmaceutical Research Institute Clinical Study Report for Protocol TRAMAP-ANAG-013: Evaluation of the efficacy and safety of tramadol/APAP in oral surgical pain. July 1999c (data on file).

26. Cooper SA, Reynolds DC, Reynolds B, et al. Analgesic efficacy and safety of (R)-ketoprofen in postoperative dental pain. J Clin Pharm 1998;38:11S-18S.

27. Roszkowski MT, Swift JQ, Pfeiffer M, et al. Opioid or acetaminophen effects on neurogenic inflammation following third molar surgery. J Oral Maxillofac Surg 1998;56(suppl 4):86-87 (abstract).

28. Breivik EK, Bjornsson GA. Variation in surgical trauma and baseline pain intensity: Effects on assay sensitivity of an analgesic trial. Eur J Oral Sciences 1998;106:844-852.

29. McNeil Consumer Healthcare Clinical Study Report for Protocol 96-626: A factorially-designed analgesic efficacy study comparing combinations of acetaminophen in doses of 325 mg, 500 mg, and 1000 mg and dextromethorphan hydrobromide in doses of 5 mg, 15 mg, and 30 mg, with the components alone and placebo in post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, November 1998 (data on file).

30. McNeil Consumer Healthcare Clinical Study Report for Protocol 96-534: A comparative study evaluating the analgesic efficacy of a single dose of acetaminophen 1000 mg, acetaminophen 1000 mg/dextromethorphan hydrobromide 30 mg, ibuprofen 400 mg, dextromethorphan hydrobromide 30 mg, or placebo in post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, July 1998 (data on file).

31. McNeil Consumer Healthcare Clinical Study Report for Protocol 95-530: A comparative study using a single dose of acetaminophen, acetaminophen/tramadol hydrochloride,

tramadol hydrochloride alone, and placebo in the treatment of post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, June 1998 (data on file).

32. RW Johnson Pharmaceutical Research Institute Clinical Study Report for Protocol TRAMAP-ANAG-003: Evaluation of the efficacy and safety of tramadol with acetaminophen (RWJ-26898-002-AQ-22) in oral surgical pain. February 1998 (data on file).

33. RW Johnson Pharmaceutical Research Institute Clinical Study Report for Protocol TRAMAP-ANAG-002: Evaluation of the efficacy and safety of tramadol with acetaminophen (RWJ-26898-002-AQ-22) in oral surgical pain. January 1998 (data on file).

34. McNeil Consumer Healthcare Clinical Study Report for Protocol 95-531: A phase IV comparative study evaluating the onset and total analgesia using a single dose of acetaminophen 1000 mg, ketoprofen 25 mg, ketoprofen 12.5 mg, or placebo in post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, August 1997 (data on file).

35. Ganry H, Insuasty JH, Schmidely N. Comparison of onset of analgesia of effervescent and noneffervescent paracetamol based on calculation rates of pain reduction. J Clin Pharm 1996;36:855 (abstract).

36. Sunshine A, Olson NZ, Marrero I, et al. Comparative analgesic efficacy of S(+) ibuprofen isomer 200 mg and 400 mg compared to acetaminophen 1000 mg in postoperative dental pain. Eighth World Congress on Pain 1996;490 (abstract).

37. Mehlisch DR, Jasper RD, Brown P, et al. Comparative study of ibuprofen lysine and acetaminophen in patients with postoperative dental pain. Clin Ther 1995;17:852-860.

38. Kiersch TA, Halladay SC, Hormel PC. A single-dose, double-blind comparison of naproxen sodium, acetaminophen, and placebo in postoperative dental pain. Clin Ther 1994;16:394-404.

39. Dolci G, Ripari M, Pacifici L, et al. Evaluation of piroxicam-beta-cyclodextrin, piroxicam, paracetamol and placebo in postoperative oral surgery pain. Int J Clin Pharmacol Res 1994;14:185-191.

40. McNeil Consumer Healthcare Clinical Study Report for Protocol 93-322: A phase IV comparative study evaluating the onset of analgesia using a single dose of acetaminophen 1000 mg, naproxen sodium 440 mg, naproxen sodium 220 mg or placebo in post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, September 1994a (data on file).

41. McNeil Consumer Healthcare Clinical Study Report for Protocol 93-321: A phase IV comparative study evaluating the onset of analgesia using a single dose of acetaminophen 1000 mg, naproxen sodium 440 mg, naproxen sodium 220 mg, or placebo in post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, September 1994b (data on file).

42. McNeil Consumer Healthcare Clinical Study Report for Protocol 91-123: A comparative study using a single dose of acetaminophen, acetaminophen/pseudoephedrine, pseudoephedrine alone, and placebo in dental pain. Fort Washington, PA: McNeil Consumer Healthcare, November 1992 (data on file).

43. Pripatnanont P, Kerdpon D, Wee CS. Postoperative pain in dental surgery. J Dent Res 1991a;70:856 (abstract).

44. Pripatnanont P, Pongpanich S. Efficacy of non-steroidal anti-inflammatory drugs in postoperative dental pain. J Dent Res 1991b;70:863 (abstract).

45. Brown P, Mehlisch D, Block E, et al. The comparative effectiveness of ibuprofen 200 mg, acetaminophen 650 mg, and placebo in postextraction dental pain. J Clin Pharm 1991;31:856 (abstract).

46. Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. Pharmacotherapy 1991;11:364-369.

47. McNeil Consumer Healthcare Clinical Study Report for Protocol 87-735: A double-blind, single dose, placebo-controlled, randomized study comparing the efficacy and safety of acetaminophen sustained release 1300 mg to regular release acetaminophen 1000 mg, naproxen 500 mg, and placebo in the treatment of post-operative dental pain. Fort Washington, PA: McNeil Consumer Healthcare, April 1991a (data on file).

48. Beaver WT, Forbes JA, Jones KF, et al. An evaluation of effervescent and noneffervescent aspirin and acetaminophen in postoperative oral surgery pain. Clin Pharmacol Ther 1990;47:164 (abstract).

49. Lehnert S, Reuther J, Wahl G, et al. The efficacy of acetaminophen (Tylenol) and acetylsalicyclic acid (aspirin) in treating postoperative pain [German]. Deutsche Zahnaerztliche Zeitschrift 1990;45:23-26 [translation provided].

50. Mehlisch DR, Sollecito WA, Helfrick JF, et al. Multicenter clinical trial of ibuprofen and acetaminophen in the treatment of postoperative dental pain. JADA 1990;121:257-263.

51. Forbes JA, Kehm CJ, Grodin CD, et al. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen-codeine combination in postoperative oral surgery pain. Pharmacotherapy 1990;10:94S-105S.

52. McNeil Clinical Study Report 88-856, A study comparing the efficacy and safety of acetaminophen sustained release 1300 mg to acetaminophen regular release 650 mg in the treatment of post-operative dental pain, 1990, (Data on file).

53. Forbes JA, Butterworth GA, Burchfield WH, et al. Evaluation of flurbiprofen, acetaminophen, an acetaminophen-codeine combination, and placebo in postoperative oral surgery pain. Pharmacotherapy 1989;9(5):322-330.

54. Cooper SA, Schachtel BP, Goldman E, et al. Ibuprofen and acetaminophen in the relief of acute pain: A randomized, double-blind, placebo-controlled study. J Clin Pharm 1989;29(11):1026-1030.

55. Beaver WT, Forbes JA, Barkaszi BA, et al. An evaluation of ibuprofen and acetaminophen in postoperative oral surgery pain. Clin Pharmacol Ther 1987;41:180 (abstract).

56. Rodrigo MRC, Rosenquist JB, Cheung LK. Paracetamol and diflunisal for pain relief following third molar surgery in Hong Kong Chinese. Int J Oral Maxillofac Surg 1987;16:566-571.

57. Sunshine A, Marrero I, Olson N, et al. Comparative study of flurbiprofen, zomepirac sodium, acetaminophen plus codeine, and acetaminophen for the relief of postsurgical dental pain. Am J Med 1986;80(suppl 3A):50-54.

58. Cooper SA, Erlichman MC, Mardirossian G. Double-blind comparison of an acetaminophen-codeine-caffeine combination in oral surgery pain. Anesth Prog 1986;33:139-142.

59. McNeil Consumer Healthcare Clinical Study Report for Protocol 3-279: A double-blind, single dose evaluation of the comparative efficacy of acetaminophen 1000 mg, ibuprofen 200 mg,

ibuprofen 400 mg, and placebo in the treatment of pain following periodontal surgery. Fort Washington, PA: McNeil Consumer Healthcare, June 1986 (data on file).

60. McNeil Consumer Healthcare Clinical Study Report for Protocol 3-234: A pilot evaluation of the analgesic efficacy and adverse effect liability of acetaminophen 1000 mg and placebo in the treatment of pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, May 1985 (data on file).

61. Skjelbred P, Løkken P, Skoglund LA. Postoperative administration of acetaminophen to reduce swelling and other inflammatory events. Curr Ther Res 1984;35:377-385.

62. Mehlisch DR, Frakes LA. A controlled comparative evaluation of acetaminophen and aspirin in the treatment of postoperative pain. Clin Ther 1984;7:89-97.

63. Forbes JA, Barkaszi BA, Ragland RM, et al. Analgesic effect of acetaminophen, phenyltoloxamine and their combination in postoperative oral surgery pain. Pharmacotherapy 1984;4:221-226.

64. McNeil Consumer Healthcare Clinical Study Report for Protocol 4-403: A double-blind single dose evaluation of the efficacy and safety of acetaminophen 1000 mg, ibuprofen 200 mg, ibuprofen 400 mg, and placebo in the treatment of pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, September 1984a (data on file).

65. McNeil Consumer Healthcare Clinical Study Report for Protocol 1-221: A double-blind, single dose evaluation of the relative analgesia and safety of acetaminophen 2000 mg, 1500 mg, 1000 mg, 500 mg, and placebo in the treatment of pain following oral or periodontal surgery. Fort Washington, PA: McNeil Consumer Healthcare, March 1984b (data on file).

66. Winter L, Appleby F, Ciccone PE, et al. A double-blind, comparative evaluation of acetaminophen, caffeine, and the combination of acetaminophen and caffeine in outpatients with postoperative oral surgery pain. Curr Ther Res 1983;33:115-122.

67. Seymour RA. Efficacy of paracetamol in reducing post-operative pain after periodontal surgery. J Clin Periodont 1983;10:311-316

68. McNeil Consumer Healthcare Clinical Study Report for Protocol 1-220: A phase IV double-blind single dose study of the safety and efficacy of acetaminophen 1000 mg, Gemnisyn 1300 mg, and placebo in the treatment of pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, November 1983a (data on file).

69. McNeil Consumer Healthcare Clinical Study Report for Protocol 2-231: A phase IV double-blind single dose evaluation of the safety and efficacy of acetaminophen 1000 mg, aspirin 650 mg, and placebo in the treatment of pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, November 1983b (data on file).

70. McNeil Consumer Healthcare Clinical Study Report for Protocol 3-251: A phase IV double-blind single dose study of the efficacy and safety of acetaminophen 1000 mg, aspirin 1000 mg, and placebo in the treatment of pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, October 1983c (data on file).

71. McNeil Consumer Healthcare Clinical Study Report for Protocol 81-229: A phase IV double-blind single dose study of the safety and efficacy of acetaminophen 1000 mg, aspirin 650 mg, and placebo in the treatment of pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, October 1983d (data on file).

72. Forbes JA, Beaver WT, White EH, et al. A new oral analgesic with an unusually long duration of action. JAMA 1982;248:2139-2142.

73. McNeil Consumer Healthcare Clinical Study Report for Protocol 0-223: A double-blind, single dose evaluation comparing the analgesic efficacy and adverse effect liability of acetaminophen 650 mg, acetaminophen 1000 mg and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, March 1982 (data on file).

74. Cooper SA, Breen JF, Giuliani RL. The relative efficacy of indoprofen compared with opioid-analgesic combinations. J Oral Surg 1981;39:21-25.

75. McNeil Consumer Healthcare Clinical Study Report for Protocol 0-214: A double-dose, single dose evaluation comparing the analgesic efficacy and adverse effect liability of acetaminophen 650 mg, acetaminophen 1000 mg and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, July 1981a (data on file).

76. McNeil Consumer Healthcare Clinical Study Report for Protocol 9-123: A phase IV double-blind study of the relative analgesic potency of orally administered Tylenol acetaminophen, aspirin and placebo tablets. Fort Washington, PA: McNeil Consumer Healthcare, September 1981 (data on file).

77. Korberly BH, Schreiber GF, Kilkuts A, et al. Evaluation of acetaminophen and aspirin in the relief of preoperative dental pain. JADA 1980;100:39-42.

78. Cooper SA, Precheur H, Rauch D, et al. Evaluation of oxycodone and acetaminophen in treatment of postoperative dental pain. Oral Surg, Oral Med and Oral Pathol 1980;50:496-501.

79. Skjelbred P, Løkken P. Paracetamol versus placebo: Effects on post-operative course. Eur J Clin Pharmacol 1979;15:27-33.

80. Winter L, Post A. Analgesic combinations with orphenadrine in oral post-surgical pain. J Int Med Res 1979;7:240-246.

81. Cooper SA, Beaver WT. A model to evaluate mild analgesics in oral surgery outpatients. Clin Pharmacol Ther 1976;20:241-250.

82. Booy RH. Relief of pain by simple analgesics in dentistry [in Dutch]. Ned Tijdschr Tandheelkd 1972;79:69-75 (English abstract).

83. Haglund B, von Bultzingslowen I. Combining paracetamol with a selective cyclooxygenase-2 inhibitor for acute pain relief after third molar surgery: A randomized, double-blind, placebo-controlled study. Eur J Oral Sci 2006;114:293-301.

84. McNeil Consumer Healthcare Clinical Study Report for Protocol 82-224: A double-blind, single dose evaluation of the comparative analgesic efficacy of acetaminophen 650 mg, acetaminophen 1000 mg, and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, June 1985 (data on file).

85. Daniels S, Reader S, Berry P, et al. Onset of analgesia with sodium ibuprofen, ibuprofen acid incorporating poloxamer and acetaminophen – a single-dose, double-blind, placebo-controlled study in patients with post-operative dental pain. Eur J Clin Pharmacol 2009;65:343-353.

86. Schachtel BP, Jungerwirth S, Wenger WC, et al. Mylagia (muscular achiness): A new placebo-controlled pain model. Clin Pharmacol Ther 1997;61:198 (abstract).

87. Gilbert MM, De Sola Pool N, Schecter C. Analgesic/calmative effects of acetaminophen and phenyltoloxamine in treatment of simple nervous tension accompanied by headache. Current Ther Res 1976;20:53-58.

88. Peters BH, Fraim CJ, Masel BE. Comparison of 650 mg aspirin and 1000 mg acetaminophen with each other, and with placebo in moderately severe headache. Am J Med 1983;74:36-42.

89. McNeil Consumer Healthcare Clinical Study Report for Protocol 84-462: A double-blind, single dose parallel study to compare analgesic efficacy and side effects profile of acetaminophen 1000 mg, ibuprofen 400 mg, ibuprofen 200 mg, and placebo in the treatment of muscle contraction ('tension') headache. Fort Washington, PA: McNeil Consumer Healthcare, July 1987 (data on file).

90. Schachtel BP, Thoden WR, Konerman JP, et al. Headache pain model for assessing and comparing the efficacy of over-the-counter analgesic agents. Clin Pharmacol Ther 1991;50:322-329.

91. Ward N, Whitney C, Avery D, et al. The analgesic effects of caffeine in headache. Pain 1991;44:151-155.

92. Furey SA, Thoden WR, Baybutt RI, et al. Aspirin 800 mg with caffeine 64 mg (asa+caf), acetaminophen 1000 mg (apap), and placebo (plc) in muscle-contraction headache. Clin Pharmacol Ther 1993;53:227 (abstract).

93. Migliardi JR, Armellino JJ, Friedman M, et al. Caffeine as an analgesic adjuvant in tension headache. Clin Pharmacol Ther 1994;56:576-586.

94. Gobel H, Fresenius J, Heinze A, et al. Effectiveness of peppermint oil and paracetamol in the treatment of tension headache [in German]. Nervenarzt 1996;67:672-681 (English abstract).

95. Schachtel BP, Furey SA, Thoden WR. Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. J Clin Pharm 1996;36:1120-1125.

96. McNeil Consumer Healthcare Clinical Study Report for Protocol 93-318: A phase IV parallel, double-blind, randomized, single-dose study comparing the analgesic efficacy and safety of acetaminophen 1000 mg/day, naproxen sodium 440 mg/day, and placebo in the treatment of tension headache. Fort Washington, PA: McNeil Consumer Healthcare, March 1997 (data on file).

97. Packman EW, Doyle G, Koronkiewicz K, et al. Onset of analgesia of ibuprofen liquigels (400 mg) compared to acetaminophen caplets (1000 mg) in the treatment of tension headache. J Clin Pharm 1998;38:876 (abstract).

98. Steiner TJ, Lange R. Ketoprofen (25 mg) in the symptomatic treatment of episodic tension-type headache: Double-blind placebo-controlled comparison with acetaminophen (1000 mg). Cephalalgia 1998;18:38-43.

99. Prior MJ, Cooper KM, May LG, et al. Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial. Cephalalgia 2002;22:740-748.

100. Steiner TJ, Lange R, Voelker M. Aspirin in episodic tension-type headache: Placebo-controlled dose-ranging comparison with paracetamol. Cephalalgia 2003;23:59-66.

101. Diener HC, Pfaffenrath V, Pageler L, et al. The fixed combination of acetylsalicylic acid, paracetamol, and caffeine is more effective than single substances and dual combination for the treatment of headache: A multicenter, randomized, double-blind, single-dose, placebo-controlled parallel group study. Cephalalgia 2005;2;5:776-787.

102. Hoernecke R, Doenicke A. Treatment of migraine attacks: The combination of dihydroergotamine tartrate and paracetamol in comparison with the mono agents and placebo [in German]. Medizinische Klinik 1993;88:642-648 [translation provided].

103. McNeil Consumer Healthcare Clinical Study Report for Protocol 97-028: A single-dose, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of acetaminophen 1000 mg for the treatment of migraine headache pain. Fort Washington, PA: McNeil Consumer Healthcare, December 2000 (data on file).

104. Lipton RB, Baggish JS, Stewart WF, et al. Efficacy and safety of acetaminophen in the treatment of migraine: Results of a randomized, double-blind, placebo-controlled, population-based study. Arch Int Med 2000;160:3486-3492.

105. McNeil Consumer Healthcare Clinical Study Report for Protocol 98-069: A single-dose, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of acetaminophen 1000 mg for the treatment of migraine headache pain. Fort Washington, PA: McNeil Consumer Healthcare, December 2000 (data on file).

106. Pendergrass PB, Scott JN, Ream LJ, et al. Effect of small doses of aspirin and acetaminophen on total menstrual loss and pain of cramps and headache. Gynecol Obstet Invest 1985;19:32-37.

107. McNeil Consumer Healthcare Clinical Study Report for Protocol 4-400: A Phase IV multicenter clinical investigation of the safety and efficacy of APAP 1000 mg (total daily dose of 4 grams), ibuprofen 400 mg (total daily dose of 1200 mg), and placebo in the management of the symptoms of primary dysmenorrhea. Fort Washington, PA: McNeil Consumer Healthcare, September 1986a (data on file).

108. Maron JJ, Ickes AC. The antipyretic effectiveness of acetaminophen suppositories versus tablets: A double-blind study. Curr Ther Res 1976;20:45-52.

109. Vargas R, Maneatis T, Bynum L, et al. Evaluation of the antipyretic effect of ketorolac, acetaminophen, and placebo in endotoxin-induced fever. J Clin Pharm 1994;34:848-853.

110. Vargas R, McMahon FG, Noveck R, et al. The antipyretic efficacy of over-the-counter (OTC) doses of ketoprofen. Clin Pharmacol Ther 1998;63:144 (abstract).

111. Pernerstorfer T, Schmid R, Bieglmayer C, et al. Acetaminophen has greater antipyretic efficacy than aspirin in endotoxemia: A randomized, double-blind, placebo-controlled trial. Clin Pharmacol Ther 1999;66:51-57.

112. Bachert C, Chuchalin AG, Eisebitt R, et al. Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: A multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour dose ranging study. Clin Ther 2005;27:993-1003.

113. Amadio P Jr, Cummings DM: Evaluation of acetaminophen in the management of osteoarthritis of the knee. Curr Ther Res 1983 Jul;34:59-66.

114. McNeil Consumer Healthcare Clinical Study Report for Protocol 3-277: A phase IV collaborative multi-clinic, double-blind study to compare efficacy of and side effects profile of acetaminophen and ibuprofen in the treatment of pain secondary to osteoarthritis. Fort Washington, PA: McNeil Consumer Healthcare, September 1986b (data on file).

115. Bradley JD, Brandt KD, Katz BP, et al: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991 Jul 11;325:87-91.

116. Lee SH, Kim SI, Yoo WH, et al. The comparison of the efficacy and gastrointestinal side effects of Tylenol-ER (extended relief) and naproxen in patients with osteoarthritis of the knee: Multicenter clinical trial. J Korean Rheum Arthritis Soc 1998 Nov;52:211-220.

117. Geba GP, Weaver AL, Polis AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: A randomized trial. JAMA 2002 Jan 2;287:64-71.

118. Wegman ACM, Van der Windt DAWM, De Haan M, et al. Switching from NSAIDs to paracetamol: A series of n of 1 trials for individual patients with osteoarthritis. Ann Rheum Dis 2003;62:1156-1161.

119. Pincus T, Koch G, Lei H, et al. Patient preference for placebo, acetaminophen (paracetamol), or celecoxib efficacy studies (PACES): Two randomized, double-blind, placebo controlled, crossover trials in patients with knee or hip osteoarthritis. Ann Rheum Dis 2004;63:931-939.

120. McNeil Consumer Healthcare Clinical Study Report for Protocol 00-103: A randomized, double-blind, placebo-controlled study evaluating acetaminophen extended release (1950 mg/day and 3900 mg/day) in the treatment of osteoarthritis of the hip or knee. Fort Washington, PA: McNeil Consumer Healthcare, April 2005a (data on file).

121. McNeil Consumer Healthcare Clinical Study Report for Protocol 98-055: A randomized, double-blind, long-term comparative study evaluating the safety and efficacy of acetaminophen (4000 mg/day) and naproxen (750 mg/day) in the treatment of osteoarthritis of the hip or knee. Fort Washington, PA: McNeil Consumer Healthcare, June 2005b (data on file).

122. McNeil Consumer Healthcare Clinical Study Report for Protocol 99-090: A four-week comparative study evaluating acetaminophen extended release (3900 mg/day) and rofecoxib (12.5 mg/day and 25 mg/day) in the treatment of osteoarthritis of the knee. Fort Washington, PA: McNeil Consumer Healthcare, February 2004 (data on file).

123. McQuay HJ, Poppleton P, Carroll D, et al. Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther 1986;39:89-93.

124. Renner B, Clarke G, Grattan T, et al. Assessment of dose dependent analgesic effects of paracetamol tablet compared to placebo. J Clin Pharm 2003;43:1038 (abstract).

125. Ragot JP. Comparison of analgesic action of mefenamic acid and paracetamol in treatment of pain after extraction of an impacted lower wisdom tooth. Inf Dent 1991;73:1659-1664.

126. Nielsen JC, Bjerring P, Arendt-Nielsen L, et al. Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol. Double-blind, placebo-controlled evaluation using painful laser stimulation. Eur J Clin Pharmacol 1992;42:261-264.

127. Hopkinson JH, Smith MT, Bare WW, et al. Acetaminophen (500 mg) versus acetaminophen (325 mg) for the relief of pain in episiotomy patients. Curr Ther Res 1974 Mar;16:194-200.

128. Yuan CS, Karrison T, Wu JA, et al. Dose-related effects of oral acetaminophen on cold-induced pain: A double-blind, randomized, placebo-controlled trial. Clin Pharmacol Ther 1998;63:379-383.

129. McNeil Consumer Healthcare Clinical Study Report for Protocol 0-223: A double-blind, single dose evaluation comparing the analgesic efficacy and adverse effect liability of acetaminophen 650 mg, acetaminophen 1000 mg, and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, March 1982 (data on file).

130. McNeil Consumer Healthcare Clinical Study Report for Protocol 0-214: A double-blind, single dose evaluation comparing the analgesic efficacy and adverse event liability of acetaminophen 650 mg, acetaminophen 1000 mg, and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, July 1981 (data on file).

131. McNeil Consumer Healthcare Clinical Study Report for Protocol 2-224: A double-blind, single dose evaluation of the comparative analgesic efficacy of acetaminophen 650 mg, acetaminophen 1000 mg, and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, April 1981 (data on file).

132. McNeil Consumer Healthcare Interim Statistical Analysis for Protocol 80-210: A phase IV double-blind study comparing the analgesic effectiveness of 1000 mg versus 650 mg of acetaminophen and placebo in episiotomy pain. Fort Washington, PA: McNeil Consumer Healthcare, June 1985 (data on file).

133. McQuay HJ, Edwards JF, Moore RA. Evaluating analgesia: The challenges. Am J Ther 2002;9:179-187.

134. Barden J, Edwards J, Moore A, et al. Single dose oral Paracetamol (acetaminophen) for postoperative pain. The Cochrane Database of Systematic Reviews 2004, Issue 1. Art No.: CD004602. DOI: 10.1002/14651858.CD004602.

135. Toms L, McQuay HJ, Derry S, et al. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. Cochrane Database of Systematic Reviews 2008, Issue 4, Art. No.: CD004602. DOI:10.1002/14651858.CD004602.pub2.

136. Moore A, Moore O, McQuay H, et al. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. Pain 1997;69:311-315.

137. Hutcheson SJ. "Pharmacodynamic modeling of the analgesic properties of specific non-opioid analgesics using the dental pain model." PhD Dissertation, University of Missouri-Kansas City, 1993.

138. Gelotte CK. Cross-study pharmacokinetic and pharmacodynamic modeling of acetaminophen: comparison of Tylenol® Extended Relief Caplets with Regular-Strength Tylenol® Caplets. Fort Washington, PA: McNeil Consumer & Specialty Pharmaceuticals; 1995. Submitted to NDA 19-872 as Phase IV Commitment.

139. Ameer B, Divoll M, Abernethy DR, et al. Absolute and relative bioavailability of oral acetaminophen preparations. J Pharm Sci 1983 Aug;72:955-958.

140. Beaulac-Baillargeon L, Rocheleau S. Paracetamol pharmacokinetics during the first trimester of human pregnancy. Eur J Clin Pharmacol 1994;46:451-454.

141. Divoll M, Ameer B, Abernathy DR, et al. Age does not alter acetaminophen absorption. J Am Geriatr Soc 1982;30:240-244.

142. Rawlins MD, Henderson DB, Hijab AR, et al. Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. Eur J Clin Pharmacol 1977;11:283-286.

143. Hindmarsh KW, Mayers DJ, Wallace SM, et al. Increased serum sulfate concentrations in man due to environmental factors: Effects on acetaminophen metabolism. Vet Hum Toxicol 1991 Oct;33:441-445.

144. Grattan T, Hickman R, Darby-Dowman A, et al. A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two

commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate. Eur J Pharm Biopharm 2000;49:225-229

145. Jorup-Rönström C, Beermann B, Wählin-Boll E, et al. Reduction of paracetamol and aspirin metabolism during viral hepatitis. Clin Pharmacokinet 1986;11:250-256.

146. Kietzmann d, Bock KW, Krahmer B et al. Paracetamol test: Modification by renal function, urine flow and pH. Eur J Clin Pharmacol 1990;39:245-251.

147. Kohli U, Sharma SK, Agarwal SS, et al. Influence of nutritional status on acetaminophen metabolism in man. Indian J Med Res 1982 Feb;75:265-273.

148. Miners JO, et al. Comparison of paracetamol metabolism in young adult and elderly males. Eur J Clin Pharmacol 1988:35:157-160.

149. Parier JL, Pichard O, Bonhomme L, et al. Bioavailability of paracetamol according to pharmaceutical form. J Pharm Belg 1988;43:287-291.

150. Yiamouyiannis CA, Harris A, Sanders RA. Paracetamol pharmacokinetics are independent of caloric intake and physical activity. Drug Invest 1994;8:361-368.

151. Altman RD. Ibuprofen, acetaminophen and placebo in osteoarthritis of the knee: A six-day double-blind study. Advances in OA Therapeutics 1999 [abstract].

152. Chopra D, Rehan HS, Mehra P, et al. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen, and betamethasone using the dental impaction pain model. Int J Oral & Maxillofac Surg 2009;38:350-355.

153. Zoppi M, Perett G, Boccard E. Paracetamol and arthritis: Placebo-controlled study of the analgesic efficacy of an effervescent formulation of 500 mg paracetamol in arthritis of the knee or hip. Eur J Pain 1995;16:42-48.

154. Koennecke HC, Leistner S. Prophylactic antipyretic treatment with acetaminophen in acute ischemic stroke: A pilot study. Neurology 2001;57:2301-2303.

155. McNeil Consumer Healthcare Clinical Study Report for Protocol 11-303: A randomized, double-blind, placebo-controlled study evaluating acetaminophen extended-release caplets (3900 mg/day) in the treatment of post-race muscle aching and pain (soreness). Fort Washington, PA: McNeil Consumer Healthcare, August 2004b (data on file).

156. Dalton Jr JD, Schweinle JE. Randomized controlled noninferiority trial to compare extended release acetaminophen and ibuprofen for the treatment of ankle sprains. Ann Emerg Med 2006;48:615-623.

157. Nielsen JC, Bjerring P, Arendt-Nielsen L. A comparison of the hypoanalgesic effect of paracetamol in slow-release and plain tablets on laser-induced pain. Br J Clin Pharmacol 1991;31:267-270.

158. Wade AG, Ward PJ. A double-blind comparison of meptazinol versus paracetamol and placebo in acute and chronic painful conditions presenting to the general practitioner. Curr Med Res Opin 1982;8:191-196.

159. Yelland MJ, Nikles CJ, McNairn N, et al. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. Rheumatology 2007;46:135-140.

160. Schnitzer TJ, Tesser JRP, Cooper KM, et al. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. Osteoarthritis and Cartilage 2009;17:1-7.

SECTION 4 ACETAMINOPHEN METABOLISM, SAFETY, AND THRESHOLD TOXICITY

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4 ACETAMINOPHEN METABOLISM, SAFETY, AND THRESHOLD TOXICITY

4.1 Key Points

Metabolism

- Acetaminophen is primarily metabolized by the liver via three pathways: glucuronidation, sulfation, and oxidation. All resulting *conjugates* from these pathways are inactive and nontoxic. Only the sulfation pathway is capacity-limited, as the glucuronide pathway does not saturate, even following a substantial acute acetaminophen overdose.

- The toxic intermediate, NAPQI,
  - is generated by the cytochrome P450 2E1 (CYP2E1) oxidation of acetaminophen;
  - is not measurable due to its high reactivity and instantaneous conjugation and detoxification with *glutathione;*
  - likely initiates a cascade of reactions after a substantial acute overdose resulting in hepatotoxicity.

- Hepatic glutathione (GSH) is
  - present in sufficient quantities to conjugate the small percent of NAPQI produced following therapeutic acetaminophen doses;
  - continuously replenished at an estimated rate of 20 to 30 μmol/min in humans, corresponding to approximately 14 g per day;
  - truly depleted when intracellular concentrations fall below 10% of normal (the critical point at which mitochondria become susceptible to oxidative stress).

- Enhanced glucuronidation with repeat dosing of acetaminophen has been
  - recognized only recently and represents a protective metabolic pathway;
  - demonstrated with repeated administration of 650-mg up to 2000-mg doses;
  - observed in studies of infants, healthy young and older adults, and adults with preexisting liver disease, including cirrhosis and Gilbert's Syndrome

- At this time, research on the evolving science of acetaminophen-protein adducts has confirmed exposure, but not the dose, timing or causal relationship to liver injury.

Safety Data from Ingestions of Repeated Maximum Therapeutic & Supratherapeutic Doses

- Retrospective safety reviews of maximum therapeutic doses
  - observed that long-term use of daily acetaminophen prescribed for chronic rheumatoid disease in 1868 (24%) and 5913 (76%) patients treated with 3000 and 4000 mg per day, respectively, are comparable in terms of safety profile when risk factors are taken into account, even in the elderly
  - observed no Hy's Law cases in 42 controlled clinical trials having $\geq$ 3000 mg daily doses of acetaminophen with durations of use from two days up to 12 months.

- Safety data from prospective studies of repeated supratherapeutic ingestions:
  - A randomized, placebo-controlled metabolism study of repeated doses totaling 6000 and 8000 mg/day for three days in young adults found increases in the liver's ability to form the nontoxic glucuronide metabolite, while not increasing the production of thiol metabolites (surrogate for NAPQI).
  - A randomized, placebo-controlled clinical trial in older adults with stroke found that repeated doses of 6000 mg/day acetaminophen for three days (n=697) were well tolerated, with only two reports of liver enzyme disturbance and no reports of liver failure.
  - A prospective, observational case series of repeated supratherapeutic overdoses suggest that the threshold for hepatotoxicity from repeated supratherapeutic ingestions over two-to-three days may be at least 8000 mg/day.

Threshold for Toxicity in the Pediatric Population

- Children under the age of 6 years are generally considered more efficient in metabolizing acetaminophen and less susceptible to toxicity than older children and adults. The most current view among medical toxicologists is that an acute accidental overdose of greater than 200 mg/kg is thought to be the threshold for toxicity in this population.

4.2 Overview of Acetaminophen Metabolism

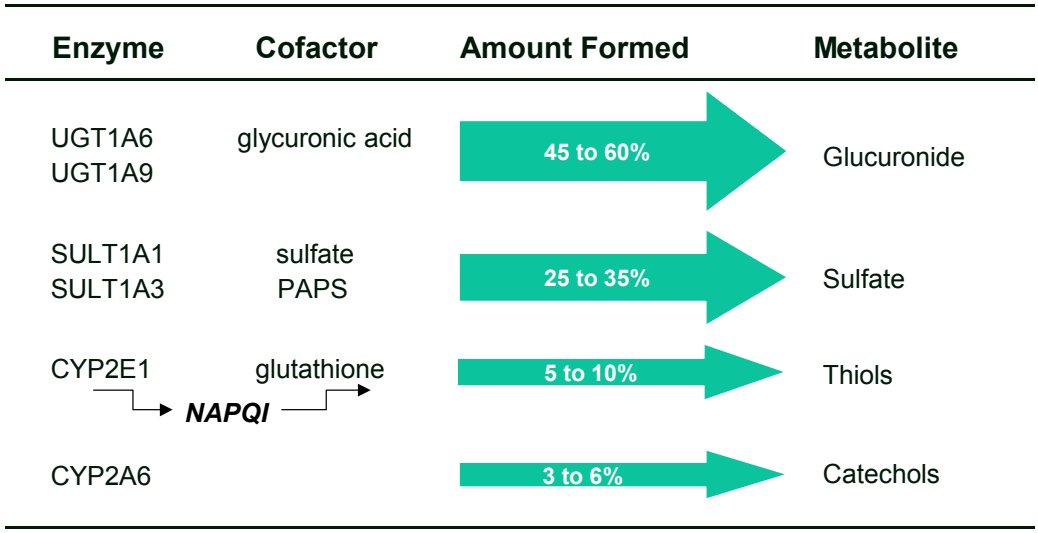
The metabolism of acetaminophen, particularly as it relates to hepatotoxicity, has been studied extensively for at least 40 years. The literature is vast and of varying scientific credibility. Despite extensive study, our understanding of the metabolic complexities of acetaminophen continues to expand with the recent unexpected discovery that acetaminophen increases its own body clearance in healthy adults when dosed repeatedly with 1000, 1500, and 2000 mg, totaling 4000, 6000, and 8000 grams per day [1].

Repeat dosing of acetaminophen was shown to increase the liver's ability to form the *nontoxic* glucuronide metabolite through enzyme induction, while not increasing the production of the toxic intermediate. This result has been observed even more recently in healthy older adults and in adults with moderate liver impairment [2], although enzyme induction in the latter group was more modest than in healthy adults. Interestingly, a comprehensive review of the literature revealed further evidence for acetaminophen induction of UDP-glucuronyltransferases (UGT) enzymes [3,4,5,6], although it was not recognized at the time nor was the implication regarding the safety of multiple days of continuous acetaminophen use.

During the last 20 years, while our understanding of mechanisms by which acetaminophen becomes toxic to hepatocytes continues to evolve, the role of liver status in the safety of acetaminophen has been the subject of scientific and medical debate. Principle topics include alcohol use, fasting, malnutrition, and preexisting liver disease. The toxicity profile of acetaminophen in acute overdoses has been well characterized [7]. Neither the parent compound, the major glucuronide and sulfate metabolites, nor the minor oxidative metabolites are potentially toxic themselves.

As illustrated in Figure 4-1, acetaminophen undergoes competitive and sequential biotransformation in which about 2% to 5% of a dose is excreted unchanged in urine. Acetaminophen is mainly conjugated with glucuronic acid by UGT enzymes, specifically the isoforms UGT1A6 and UGT1A9 [8,9]. It is also a substrate for two sulfotransferases, SULT1A1 and SULT1A3 [10,11]. Sulfation of acetaminophen is partly governed by the availability of inorganic sulfate, which is rate limiting in the formation of the cofactor of sulfation, 3'-phosphoadenosine-5'phosphosulfate (PAPS). The other rate-limiting reaction is sulfotransferase activity. A small fraction of an acetaminophen dose is oxidized by cytochrome P4502A6 (CYP2A6) to form stable nontoxic catechols eventually found in the urine as sulfate and glucuronide conjugates [12].

Figure 4-1 Acetaminophen Metabolism†



† The balance of an acetaminophen dose is excreted as acetaminophen in the urine.

About 5% to 10% of an acetaminophen dose is oxidized by cytochrome P4502E1 (CYP2E1) to produce N-acetyl-p-benzoquinoneimine (NAPQI) [13], a highly reactive, short-lived electrophile, which is subsequently conjugated with glutathione. This conjugate is then cleaved to result in chemically stable, nontoxic thiol metabolites: the cysteine, mercapturate, methylthio, and methanesulfinyl adducts of acetaminophen. The contribution of CYP isoenzymes, other than CYP2E1, to NAPQI formation is negligible *in vivo* in humans and is clinically insignificant [14].

4.2.1 Metabolism Aspects of Acute Overdose Ingestions

Clinical evidence demonstrates that the hepatic glucuronidation capacity for metabolizing acetaminophen is not saturated, even among those individuals who have taken considerable overdoses. If hepatic dysfunction is observed, hepatic metabolism, including glucuronidation, is slowed, but glucuronidation is not saturated [15,16] in the Michelis-Menten manner. The reported urinary excretion of the glucuronide metabolite ranges from 45% to 60% of therapeutic doses and from 40% to 75% of overdoses above 137 mg/kg (approximately 10 g) [17,18]. However, sulfate conjugation is capacity-limited at higher doses as evidenced by a decrease in the fractional urinary excretion of sulfate metabolites [19]. The mechanism seems to be depletion of activated sulfate for conjugation and, perhaps, actual saturation of the enzyme at very high doses.

Because of the limited capacity of sulfation at higher doses, the fraction of an acetaminophen dose metabolized by glucuronidation and CYP2E1 oxidation to NAPQI would increase. Normally there is ample glutathione present to account for this increase. As hepatic glutathione is consumed by NAPQI, it is continuously replenished at an estimated rate of 20 to 30 μmol/min in humans, corresponding to approximately 14 g per day [40,41,39]. Therefore, the rate of consumption must substantially exceed this rate of production for an appreciable period to cause enough depletion of glutathione to allow necrosis to occur from free NAPQI.

The exact mechanisms by which NAPQI causes hepatocellular death are not completely understood, but seem to include oxidative stress, loss of function of critical macromolecules due to NAPQI adduct formation, blebbing of the cellular and mitochondrial membranes, and loss of calcium homeostasis. The resulting hepatocellular necrosis is observed centrilobularly. The antidote, N-acetylcysteine (NAC), replenishes glutathione and protects against necrotic cell death if administered early enough in the sequence of events [7,20].

4.2.2 Acetaminophen Protein Adducts

The determination of drug–protein adducts can help with the establishment of dose–toxicity relationships, although the relationship between drug bioactivation, level of protein adducts and the occurrence of organ injury is not simple [21]. The formation of drug–protein adducts may be nontoxic, moderately toxic, or fatal, which depends on the drug, kinetics of drug–protein adduct formation and degradation, affected proteins and organs, and pathological conditions of the patients [22]. Several commonly used drugs have been found to form protein adducts after being activated, and these include acetaminophen, aspirin, erythromycin, ibuprofen, propranolol, lidocaine, tacrine, and valproic acid [21,22].

As reviewed in the previous section, acetaminophen hepatotoxicity is mediated through the reactive metabolite intermediate, NAPQI, which can readily conjugate to cellular proteins when sufficient amounts of glutathione are not available during an excessive acetaminophen overdose. A specific protein-adduct, 3-para cysteinyl acetaminophen, has been investigated as a potential marker for acetaminophen hepatotoxicity in patients with acute liver failure [23,24]. However, studies in normal and knockout mice point to the importance of inflammatory processes in development of hepatoxicity [25,26].

In a review of published studies of acetaminophen protein adducts in patients, Bond [27] concludes that available data are inadequate at present to suggest the routine use of 3-para cysteinyl acetaminophen as a marker of hepatotoxicity. Its appearance in the serum

parallels that of other serum liver injury markers generated from routine liver function laboratory tests. Hence, it is unlikely to be an early predictor of acetaminophen-induced hepatotoxicity and guide therapeutic interventions. Moreover, he cites other studies [28] that found "adduct formation and release occurs in adults taking therapeutic doses of acetaminophen in the absence of liver injury, but that these values are very low compared to those experiencing acetaminophen induced hepatotoxicity." Bond concludes that the presence of an acetaminophen-protein adduct confirms exposure, but not dose, timing or causal relationship to liver injury at this time [27].

Other data summarized in Bond's review [27] include a retrospective analysis of frozen serum samples from 66 patients with acute liver failure and 15 patients with acetaminophen overdose but no overt hepatotoxicity [23]. The investigators report that the presence or absence of hepatic injury serum markers paralleled the overdose or absence of acetaminophen as a causative factor in hepatotoxicity. Although, this provides evidential support to serum markers as associated with hepatic injury, these data cannot prove causality.

In pediatric patients with acute liver failure [24], there was no statistical difference between patients with acetaminophen-associated hepatic failure and subjects with hepatic failure due to indeterminate causes. The results raise questions about adducts serving as sensitive and specific markers of hepatotoxicity. It is possible that the hepatotoxicity cases reported as being unrelated to acetaminophen were either related and misreported or acetaminophen dosing following liver failure caused the adducts to be formed and detected in the serum.

4.2.3 Estimation of the Acute Hepatotoxic Dose of Acetaminophen

The theoretical estimates that about 70% to 90% of hepatic glutathione stores need to be consumed to cause hepatotoxicity in humans following an *acute overdose* are extrapolated from acute overdose data in mice and hamsters [29]. True depletion of hepatic glutathione, defined as an intracellular concentration below 10% of normal (the critical point at which mitochondria become susceptible to oxidative stress), has not been documented in humans aside from states of intoxication by some drugs, including excessive overdoses of acetaminophen [30].

To estimate the threshold dose for hepatic toxicity following an acute overdose, Mitchell et al [31] used data from a study in adults that found the amount of glutathione conjugates formed with 900, 1200, and 1800 mg doses of radiolabeled acetaminophen was about 4%.

Assuming the lower level of 70% depletion of glutathione as mice and assuming that the average 1.5-L liver for a 70 kg person contains 6 mmol of glutathione, at least 4 mmol of NAPQI would be necessary to cause hepatic injury in humans. Therefore, the amount of acetaminophen estimated to generate this much NAPQI is 15 g taken all at once as an acute overdose: (4 mmol)(acetaminophen 151.2 mg/mmol) / 4%.[1]

However, the theoretical estimate of 15 g of acetaminophen as the acute hepatotoxic dose in humans by Mitchell et al does not account for the dynamics of hepatic glutathione turnover. There is a prompt increase in glutathione synthesis signaled by the consumption of hepatic glutathione stores. In mice, the rate of synthesis became faster than the rate of consumption at 90 minutes following a toxic dose of 300 mg/kg of acetaminophen [29]. Hepatic production of glutathione in humans is estimated at approximately 1.62 mmol/h for a liver weight of 1500 g [40,41,39]. Therefore, theoretically, an additional 1.62 mmol of hepatic glutathione would be produced each hour, which would be available to consume the amount of NAPQI that may be generated from an additional 6 g acetaminophen.

Adding together the original 15 g acetaminophen based on the assumption that 70% depletion of hepatic glutathione stores leads to hepatotoxicity, and the 6 g from the stimulation of cysteine and glutathione turnover rates, the estimated theoretical acute dose for acetaminophen hepatotoxicity is approximately 21 g taken all at once as an acute overdose for a 70 kg person (and 15 g for a 50 kg person).

This range of theoretical estimates is comparable to those estimated by Prescott [15] from overdose clinical outcomes in humans. The threshold dose for hepatotoxicity following acetaminophen overdose was estimated from a collection of overdose cases in which patients were cared for using supportive therapy. The amount of acetaminophen absorbed was estimated by multiplying the plasma acetaminophen concentration measured at three hours after ingestion with the distribution volume of acetaminophen (0.8 L/kg), and these amounts were paired with the liver damage ratings for all cases. The results indicate that the threshold dose for hepatotoxicity in humans is approximately 250 mg/kg taken all at once, which corresponds to 12.5 and 17.5 g for a 50 and 70 kg person, respectively.

[1] Mitchell et al [31] rounded the amount of NAPQI generated from 4.2 to 4 mmol in their calculations (70% of 6 mmol equals 4.2 mmol). In the review article by Rumack [7], 4.2 mmol NAPQI is used in the same calculations, resulting in a 15.9 g acetaminophen dose taken all at once in an overdose.

4.2.4 Single-Dose Pharmacokinetic Studies in Volunteers Given up to 9 Grams to Simulate Acute Overdose

Data from prospective pharmacokinetic studies in which acetaminophen was given to volunteers in excess of maximum labeled doses[2] provide an estimate of what degree of overdose can be tolerated without developing hepatic injury. These studies were designed to simulate acute overdoses[3] using single doses from 2.8 to 9.1 g within a well-controlled study environment in order to determine absorption differences between dosage forms [32,33] and assess various overdose interventions [34,35,36,37,38]. Information on the control groups without absorption interventions (eg, activated charcoal and lavage) are highlighted below, because they provide information about those instances when an individual takes more than a 1 g dose of acetaminophen.

Overall, 80 subjects in these pharmacokinetic studies ingested from 2.8 to 9.1 g of acetaminophen on more than one occasion because of the crossover design, which totaled 152 exposures of single supratherapeutic doses. An additional 120 exposures included co-administration with activated charcoal. Across studies, the maximum plasma concentrations of acetaminophen attained over the range of doses were below the threshold of 200 µg/mL for toxicity and NAC treatment in the Rumack acute overdose nomogram. The apparent elimination half-life ranged from 2.2 to 2.6 hours, which is similar the elimination rate of therapeutic doses. These data demonstrate that single doses of up to 9 g taken as an acute overdose were well tolerated with no serious adverse events or discontinuations reported

4.3 Repeated Therapeutic Ingestions Up to Maximum-Labeled Dose

4.3.1 Glutathione Repletion with Repeat or Chronic Dosing

When the overdose is not taken all at once but rather is divided over an entire day, continuous glutathione synthesis provides an additional 1.62 mmol of hepatic glutathione per hour[4] to the pool available to detoxify NAPQI, the reactive acetaminophen metabolite [39,40,41]. As hepatic glutathione is consumed by NAPQI, it is continuously

[2] Therapeutic doses of 650 and 1000 mg correspond by body weight to 13 and 20 mg/kg, respectively, for a 50 kg (110 lb) person, and 8.7 and 13.3 mg/kg for a 75 kg person (165 lb).

[3] Acetaminophen doses were administered to subjects in one of two ways: (1) a specific number of tablets, equal to 5 g for example, which results in a range of mg/kg doses, or (2) a specific mg/kg dose, equal to 75 mg/kg for example, which results in a range of tablets or grams based on each subject's body weight.

[4] Estimate for a 70 kg person.

replenished at an estimated rate of 20 to 30 μmol/min in humans, corresponding to approximately 14 g per day. Therefore, the rate of consumption must substantially exceed this rate of production for an appreciable period to cause enough depletion of glutathione to allow significant hepatotoxicity to occur from free NAPQI.

Replenishment of glutathione begins immediately after taking a therapeutic dose of acetaminophen [30], stimulated by decreasing concentrations of reduced hepatic glutathione during detoxification of NAPQI. Hepatic glutathione concentrations may decrease by less than 10% after a 1000-mg dose, and that they rapidly recover because of increased synthesis. With repeat dosing of acetaminophen every six hours, the associated fluctuations in glutathione concentrations may also stimulate glucuronidation by shifting glycogen metabolism toward UDP-glucose formation, which was shown *in vitro* to stimulate both ascorbate synthesis and glucuronidation [42].

4.3.2 Favorable Changes in Acetaminophen Metabolism with Repeat Dosing, Consistent Across Dose Levels and Different Populations

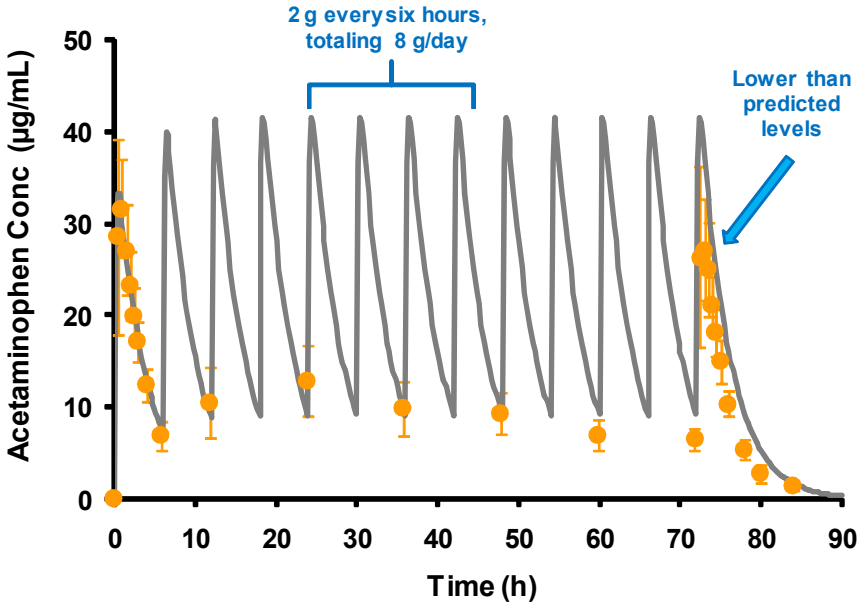
Regarding the safety of multiple days of continuous acetaminophen use, prospective pharmacokinetic studies of repeat dosing in infants [3], healthy young [1,4,5] and older adults [2], and in adults with preexisting liver disease [2,6], show that acetaminophen plasma concentrations

- reach steady-state levels within 24 hours;
- do not accumulate to higher levels with continued dosing, but rather are lower than expected due to increased body clearance of acetaminophen; and
- undergo enhanced metabolism to the nontoxic glucuronide conjugate.

These results are consistent with the short elimination half-life of two to three hours for acetaminophen and the recommended dosing interval of four to six hours.

Increases in the body clearance of acetaminophen through enhanced glucuronidation were observed in a study of healthy young adults who were dosed repeatedly with 1000, 1500, and 2000 mg every six hours for three days [1]. Body clearances increased from about 20% to 30% for all dose levels studied, and these changes were each statistically significant at $p < 0.0001$. In addition, plasma concentrations of the nontoxic glucuronide metabolite were higher after repeat dosing than would predicted from single-dose pharmacokinetic data. Figure 4-2 shows mean plasma concentrations after 13 doses of 2000 mg acetaminophen, which illustrates that acetaminophen does not accumulate, but instead decreases over time due to increasing body clearance.

Figure 4-2 Acetaminophen Concentrations are Lower than Predicted Due to Increases in Clearance for Subjects Taking 8000 mg/day as 2000-mg Doses



4.3.3 Enhanced Glucuronidation with Repeat Dosing – A Protective Metabolic Pathway

Enhance glucuronidation has only been recognized recently with repeat dosing of acetaminophen and represents a protective metabolic pathway. Increasing glucuronidation prevents further oxidation of agents, such as acetaminophen, protecting cells from the generation of toxic electrophilic compounds and from the consequent progressive lowering of the cellular reduced glutathione pool. Thus, this mechanism may serve as a useful protective pathway in the liver [42].

This favorable change of increased glucuronidation of acetaminophen with repeat dosing has been observed across dose levels from 650 mg up to 2000 mg per dose and across different populations. A comprehensive review of the literature revealed further evidence for increased acetaminophen glucuronidation with repeat dosing [4,5,6], although it was not recognized at the time or its potential implications in the safety and tolerability of multiple days of continuous acetaminophen use. These studies are summarized in Table 4-1, and briefly described below.

Table 4-1 Repeat Dosing of Acetaminophen Induces Glucuronidation - A Protective Metabolic Pathway

Population	N	Age (y)	Dose (mg)	Regimen	Evidence of Induced Glucuronidation
Neonates [3]	18	39 wks (23-40)	10[a] mg/kg	Every 6-8 h for 1-4 days	↑ urinary G/T ratio with consecutive urine collections
Young Adults [1]	24	26 (5.7)	1000	Every 6 h for 3 days	plasma glucuronide ratio ↑ 44% from first to last dose
Young Adults [1]	12	27 (6.6)	1500	Every 6 h for 3 days	plasma glucuronide ratio ↑ 32% from first to last dose
Young Adults [1]	12	25 (5.0)	2000	Every 6 h for 3 days	plasma glucuronide ratio ↑ 89% from first to last dose
Young Adults [4]	9	22.4 (4.5)	650	Every 6 h for 5 doses	glucuronide urine excretion ↑ from 47.7% to 55.6 % of the acetaminophen dose
Young Adults [5]	8	22.6 (3.5)	650	Every 6 h for 5 doses	glucuronide urine excretion ↑ from 56.1% to 61.5 % of the acetaminophen dose
Older Adults [2]	13	50.5 (5.2)	1000	Every 6 h for 4 days	glucuronide urine excretion ↑ from 49% to 60% of the acetaminophen dose
Adults with Cirrhosis [2]	12	49.9 (4.8)	1000	Every 6 h for 4 days	glucuronide urine excretion ↑ from 40% to 53% of the acetaminophen dose
Adults with Gilbert's Syndrome [6]	2	nr	1500	Every 6 h for 5 days	glucuronide urine excretion ↑ from 37% to 59% and 45% to 62% of the acetaminophen dose

a: After a loading dose of 15 mg/kg, 10 mg/kg doses administered; urinary G/T ratio (glucuronide/ total acetaminophen) excreted; nr – not reported

In a study of healthy adults, the amount of glucuronide metabolite excreted in urine increased from 47.7 ± 9.3% after a single 650-mg dose to 55.6 ± 6.8% ($p < 0.05$) after a regimen of 650 mg acetaminophen every six hours [4]. A similar increase in urinary glucuronide metabolite was reported in another group of healthy subjects dosed with 650 mg acetaminophen every six hours [5].

In an early study of two adults with Gilbert's Syndrome, metabolites were measured after an intravenous 10-mg/kg dose of acetaminophen was administered before and again after 20 oral doses of 1500 mg acetaminophen [6]. The amount of glucuronide excreted in the urine increased from 37% to 59% and 45% to 62% of the acetaminophen dose for each subject, respectively.

In a metabolism study of neonates [3], 10 mg/kg acetaminophen was administered intravenously after a loading dose of 15 mg/kg, every six hours for infants with a postconceptional age of > 36 weeks or every eight hours with a postconceptional age ≤ 36 weeks. The clinical investigators documented a significant effect of repeated administration of acetaminophen on increasing UGT activity in the 18 neonates with consecutive urine metabolite collections. This observed effect remained significant in a multiple linear regression model to correct for the effect of postnatal and postconceptional age [3].

In a recent metabolism study of adults with preexisting liver disease (cirrhosis due to alcohol abuse, hepatitis C, or both) and matched control subjects [2], increases in body clearance of acetaminophen were found with repeat dosing of 1000 mg every six hours for four days. On average, body clearance increased 14% ($p = 0.037$) in the liver-impaired group and 27% ($p = 0.0001$) in the matched-control group. This change was accompanied by an increase in the fraction of acetaminophen dose excreted as the nontoxic glucuronide metabolite, despite an expected decrease in the sulfate metabolite. Specifically, the amount of glucuronide produced increased from 40.2 ± 13.3% to 52.1 ± 16.4% in the liver-impaired subjects ($p < 0.001$) and from 49.0 ± 7.4% to 60.8 ± 11.1% in the control subjects ($p = 0.008$). No statistical differences were detected between groups using one-way analysis of variance, indicating similar responses to repeat dosing of 1000 mg every six hours in both the diseased and healthy liver.

4.3.4 Retrospective Safety Reviews of Repeated Dosing at 3000 or 4000 mg/day

4.3.4.1 Retrospective Study of Medical Records of Long-Term Acetaminophen Use

In a observational study [43], the hepatic and renal safety profiles of two daily dosage regimens of acetaminophen (3000 and 4000 mg) in patients with chronic rheumatoid diseases were compared using data extracted from computerized medical records. Two groups of patients from the United Kingdom (UK) were compared with regard to available variables, including demographic information, the presence or absence of alcoholism, accompanying diseases, and the occurrence of hepatic and renal adverse events. Table 4-2, which is extracted from the published report, summarizes main characteristics of the study population and results. A decision tree method was used to determine those variables that would best enable the occurrence of a hepatic or renal adverse event to be explained.

Table 4-2 Characteristics of the Study Population and Results [43]

Parameter			Acetaminophen 3000 mg/day	Acetaminophen 4000 mg/day
			n (%)	n (%)
Patients			1868 (24.0)	5913 (76.0)
Gender	Female		1337 (71.6)	4240 (71.7)
	Male		531 (28.4)	1673 (28.3)
Age (years)	Mean		72.5	73.1
	sd		(11.9)	(11.1)
Alcoholism	Presence		181 (9.7)	561 (9.5)
	History		12 (0.6)	36 (0.6)
	Absence		1675 (89.7)	5316 (89.9)
Number of acetaminophen prescriptions		Mean	13.0	11.9
		sd	(15.6)	(14.9)
Total duration of exposure to acetaminophen (days)		Mean	277	201
		sd	(377)	(278)
Suspension of treatment due to adverse events (regardless of the etiology) and reaction attributable to acetaminophen:		n(%)	11 (0.59)	17 (0.29)
Patients with at least one hepatic and/or renal adverse event potentially linked to acetaminophen:		n(%)	16 (0.86)	40 (0.68)

Among the 7781 patients identified as having been prescribed acetaminophen for chronic rheumatoid diseases, 1868 (24%) and 5913 (76%) were treated with 3000 and 4000 mg per day, respectively. The mean overall duration of exposure to acetaminophen was 277 days in the 3000-mg group and 201 days in the 4000-mg group.

The analyses showed no statistical differences between the two treatment groups with respect to age, gender, and the presence of accompanying alcoholism. The number of patients having stopped treatment due to the occurrence of an adverse event (regardless of the etiology) or having had a reaction attributable to acetaminophen was not significantly different between the groups receiving 3000 and 4000 mg per day (odds ratio 0.49; 95% confidence interval 0.23-1.04). No statistical difference was observed for the percentage of patients with hepatic and/or renal type adverse events potentially linked to acetaminophen intake (0.86%: 3000-mg group vs. 0.68%: 4000-mg group).

The investigators conclude that daily doses of 3000 mg and 4000 mg acetaminophen prescribed for long-term treatment of chronic rheumatoid disease are comparable in terms of safety profile when risk factors are taken into account, even in the elderly [43]. They summarized limitations with this study that include

- under-reporting by the general practitioner of the number of prescriptions issued for a treatment with acetaminophen;
- patients may not necessarily have purchased the treatment prescribed;
- patients often take acetaminophen without a prescription since it is available in pharmacies over the counter;
- uncertainty that the treatment will be taken according to the particular indications, which could lead to poor compliance or overconsumption;
- under-reporting of adverse events if the general practitioner does not consider them to be relevant;
- under-reporting of an adverse event that may too severe, requiring hospitalization or prompting direct contact with a specialist and/or consultation in a hospital setting.

4.3.4.2 Retrospective Analysis of Controlled Clinical Trials for Cases of Hy's Law

Hy's Law [44,45] is generally accepted as a safety biomarker indicative of drug-induced hepatotoxicity that carries with it at least a 10% mortality rate. Requirements for Hy's Law reflect both hepatocellular injury and loss of hepatic function. It defines drug-induced hepatotoxicity as cases presenting with increased aminotransferase activities (ALT, AST) of $\geq$ 3 times the upper limit of reference range (3 x ULRR) in treated versus untreated patients; and increased bilirubin at a rate of $\geq$ 2 x ULRR. In addition, there should be no evidence or cause of biliary obstruction or hepatocellular injury (eg, no viral hepatitis, concomitant use of other hepatotoxic drugs, recent marked hypotension, congestive heart failure especially right sided) other than investigative drug.

Safety data were reviewed for cases meeting Hy's Law from randomized, controlled clinical studies that were conducted by McNeil and its affiliated companies using the following selection criteria:

- Minimum of 3 days multiple dose administration of acetaminophen-containing product
- Minimum dose of 3000 mg/day

This review excluded any short duration (single dose studies or studies with dosing less than three days) dental pain or episiotomy studies, and studies that did not include liver function test measurements both pre- and post-dose. However, adverse event data from

the excluded studies have been reviewed, and no cases of any hepatic dysfunction indicative of hepatotoxicity were identified.

Thirty (30) studies met the review criteria, including five studies with previously published data [46]. In these studies, approximately 3852 subjects received multiple doses of acetaminophen at doses of 3000 mg/day or higher for three or more days. Transient elevations in ALT and/or AST were observed in some cases but these resolved spontaneously. None of the ALT and/or AST elevations, when > 3 x ULRR were accompanied by increases in total bilirubin of > 2 x ULRR, and none met the threshold of Hy's Law. No cases of hepatic failure or other significant liver injury were observed.

An additional 14 published clinical trials evaluating the efficacy and safety of acetaminophen at doses of 3000 mg/day or higher were identified and reviewed if they reported data from liver function tests. Multiple-doses were taken for durations from two days up to six weeks, with approximately 2374 subjects treated with acetaminophen. Although transient elevations in ALT and/or AST were reported, no cases met the threshold of Hy's Law.

This retrospective review has limitations with regard to generalizing safety to the entire population, because the clinical trials may have excluded subjects who have pre-existing liver disease or other accompanying conditions, or clinical laboratory values outside of the reference ranges at screening. Another limitation is that clinical trial subjects are more closely monitored during drug treatment, and may be discontinued early by the investigator with initial observations of particular adverse events.

4.4 Repeated Supratherapeutic Doses > 4000 mg/day in Adults

A chronic overdose is termed a repeated supratherapeutic overdose to differentiate it from chronic therapeutic use. Ingestion of a dose greater than the maximum-labeled daily dose of 4000 mg over a period greater than eight hours is considered a repeated supratherapeutic overdose. This may occur by taking a single product or a combination of OTC and/or prescription products containing acetaminophen. A few prospective studies evaluated situations where doses of acetaminophen greater than the maximum-labeled daily dose have been taken, and are highlighted in this section.

4.4.1 Prospective Metabolism Study Evaluating the Hepatotoxic Potential of Repeated Supratherapeutic Doses of Acetaminophen

With regard to making comparisons between toxicity from acute overdoses and toxicity from repeated supratherapeutic overdoses, prospective pharmacokinetic and metabolism studies suggest that the hepatotoxic potential may be less when the overdose is divided over an entire day (repeated supratherapeutic overdose) than when the overdose is taken all at once (acute overdose). The tolerability of repeated supratherapeutic doses totaling 6000 or 8000 mg/day has been evaluated in healthy volunteers [1,47]. This multiple-dose pharmacokinetic study had a randomized, double-blind, placebo-controlled, parallel-group design with three dosing regimens. Healthy subjects received repeated doses of acetaminophen (1000 then 1500 mg, or 1000 then 2000 mg, every six hours) or placebo over three days of continuous use. The disposition of acetaminophen and its metabolites, and the tolerability of acetaminophen doses greater than the maximum-labeled daily dose were characterized.

AST and ALT activities measured throughout the study were consistent across the 4000, 6000, and 8000 mg/day acetaminophen dose levels and with placebo. Serum aminotransferase activities did not exceed the ULRR, except for one subject with an AST of 43 U/L (ULRR, 42 IU/L), which was not considered clinically significant. There were no increases in bilirubin.

All doses were generally well tolerated. The incidence and frequency of adverse events were generally mild, and similar across the daily acetaminophen doses and when compared with placebo. The most frequently reported adverse events were headache (six subjects: three receiving 8000 mg/day and three randomized to placebo); dizziness (five subjects: three receiving 4000 mg/day, one receiving 8000 mg/day, and one randomized to placebo); and nausea (five subjects: one receiving 4000 mg/day, one while receiving both 4000 and 6000 mg/day, one receiving 8000 mg/day, and two randomized to placebo). Overall, in this multiple-dose study of 4000, 6000, and 8000 mg/day of acetaminophen for three days, several aminotransferase determinations demonstrated no clinically important elevations at 1, 1.5, or 2 times the maximum-labeled acetaminophen dose.

4.4.2 Clinical Trial of Repeated Supratherapeutic Acetaminophen (6000 mg/day) in an Off-Label Indication

A multicenter, randomized, double-blind, placebo-controlled trial was recently published on the use of supratherapeutic doses of 6000 mg/day acetaminophen to assess whether early treatment improves functional outcome in subjects with acute stroke by reducing body temperature and preventing fever [48]. Although subjects were excluded if they had a

history of liver disease or alcohol abuse, or high concentrations of liver enzymes (more than twice the ULRR), this trial enrolled an older compromised population of adults with the average age of 69.8 ± 13.0 years.

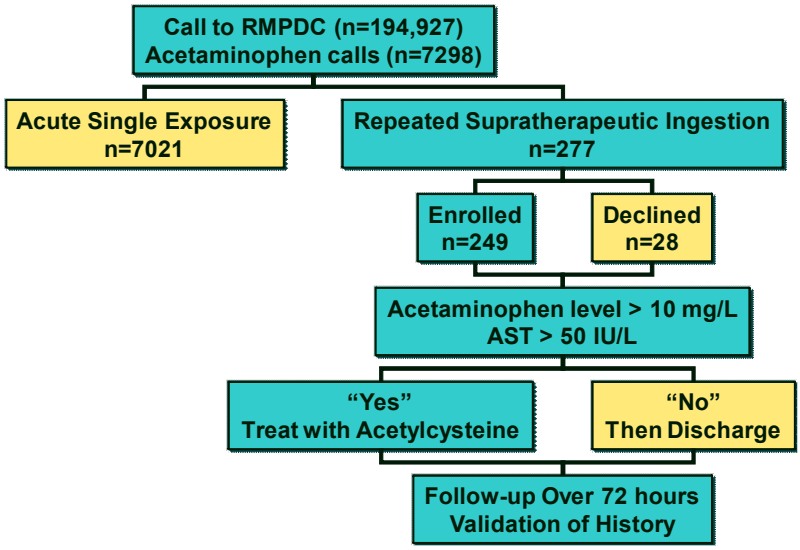
Subjects with acute stroke were randomly allocated acetaminophen (n=697) or placebo (n=703) given orally or rectally. Subjects treated with acetaminophen received a dose of 1000 mg six times daily for three days. Of the subjects treated with acetaminophen, 78% (546/697) completed the three days. This supratherapeutic dose was well tolerated, with only two reports of liver enzyme disturbance and no reports of liver failure [48]. Overall, the number of serious adverse events in both treatment groups was similar.

4.4.3 Prospective Case Series for Repeated Supratherapeutic Doses of Acetaminophen

Information has become available on the epidemiology, medical assessment, and clinical course of repeated supratherapeutic overdoses of acetaminophen. Two prospective case series of repeated supratherapeutic overdoses have been recently reported, one from the US [49] and the second from the UK [50].

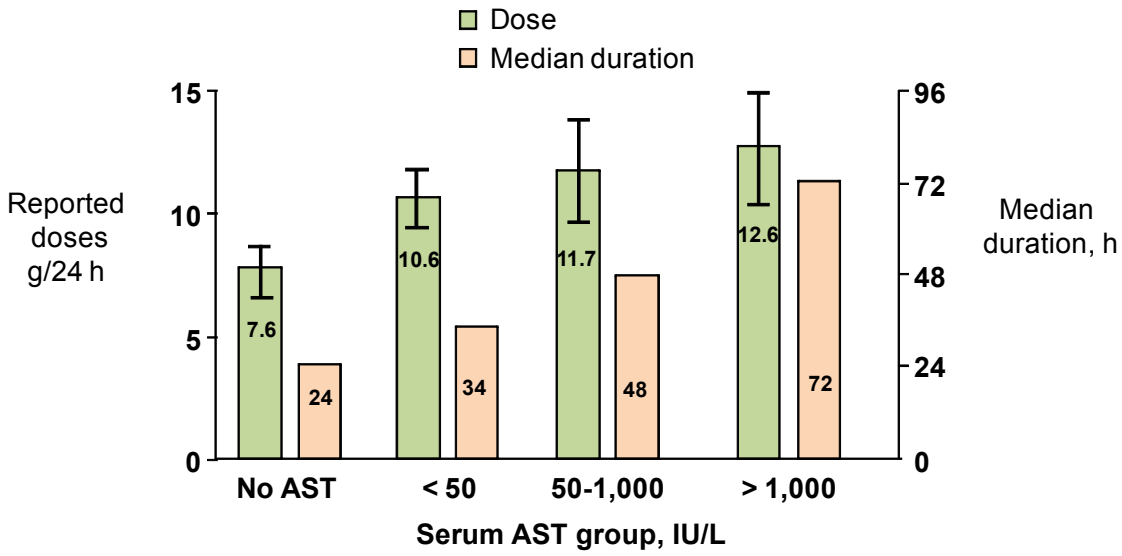
The US prospective case series, which was designed to characterize the potential toxicity profile of acetaminophen in individuals with repeated supratherapeutic overdose managed by a poison control center, provides some important insights into the potential threshold for toxicity [49]. In the study outline shown in Figure 4-3, two groups of patients were identified based upon clinical presentation: (1) those with elevated AST on presentation were separated into two levels of severity; and (2) those with normal AST on presentation. Of 277 patients eligible, 249 patients were enrolled. At presentation, serum AST levels less than 50 IU/L were found in 126 cases, AST 50 to 1,000 IU/L in 47 cases, and AST above 1,000 IU/L in 37 cases. No AST data were available for 39 cases.

Figure 4-3 Flow Chart of Study Population



The results in Figure 4-4 show that subjects with an AST level less than 50 IU/L ingested a mean reported dose of acetaminophen of 10.6 g per 24 hours (95% CI 9.4 to 11.7 g per 24 h) for a median duration of 34 hours. For subjects with admission AST levels between 50 and 1000 IU, the mean reported dose of acetaminophen was 11.7 g per 24-hour period (95% CI 9.6 to 13.8 g/24 h) for a median duration of 48 hours. For subjects with AST levels greater than 1,000 IU/L at presentation, the mean reported dose of acetaminophen was 12.6 g per 24 hours (95% CI 10.3 to 14.9 g/24 h) for a median duration of 72 hours.

Figure 4-4. Mean (95% CI) Reported Dose (g) of Acetaminophen Consumed by Group of Subjects Sorted by AST Activity at Enrollment



No subject with an AST level below 50 IU/L at presentation developed hepatotoxicity (defined as AST >1,000 IU/L). All subjects who developed hepatotoxicity presented with AST above 50 IU/L. Seven (15%) subjects with AST levels between 50 to 1,000 IU/L at presentation subsequently developed hepatotoxicity; one subject died. Six (16%) subjects with AST levels above 1,000 IU/L at presentation died or received liver transplants. The authors conclude that patients who present after repeated supratherapeutic overdoses and have normal liver function at presentation may not need treatment with N-acetylcysteine (NAC), and that injury caused by acetaminophen repeated supratherapeutic ingestion is related to dose magnitude and duration [49]. These data suggest that the threshold for hepatotoxicity for repeated supratherapeutic ingestions over two-to-three days may be at least 8 g/day.

The study of UK case series was based on a prospective survey of all calls regarding acetaminophen poisoning to the London-based National Poisons Information Service for the period May to August 2000 [50]. Of 280 calls received, 19 were unintentional (6.8%) and 261 were intentional (93.2%). The mean reported acetaminophen dose ingested for the unintentional cases was 17.7 g (range 8-32 g), and the mean time from the first acetaminophen dose to presentation was 32 hours. Notably, in this case series none of the 19 patients developed serious sequelae, although 17 required treatment with NAC.

4.5 Threshold of Overdose Toxicity in Pediatric Population

4.5.1 Threshold Dose Influenced By Age-Dependent Metabolism

The relative safety in acute acetaminophen overdose seen in younger children, under 6 years of age, has been attributed to age-related differences in metabolism, early discovery, and appropriate treatment [51]. The clearance mechanisms of acetaminophen have been studied along the continuum of ages from fetal to infants through childhood and adults. Clearance mechanisms mature and change through different phases of life, and for acetaminophen, adult patterns of metabolism are reached between 10 and 12 years of age. It appears that for neonates and young children (Table 4-3), sulfation (S) may be the most important clearance mechanism for acetaminophen, with glucuronidation (G) being lower as is evidenced by the smaller G:S ratios [52,53]. In contrast, glucuronidation is higher than sulfation in older children and adults. Both glucuronidation and sulfation are direct conjugation metabolic pathways for acetaminophen accounting for about 80 to 85% of a dose.

Table 4-3 Metabolism and Elimination of Acetaminophen in Pediatric Population

Population	N	Age range	Dose	T½ (h)[a]	Metabolism Summary
Neonate [52]	12	2-3 day old, full term	12 mg/kg, SD, oral	3.5 (0.85)	Urinary excretion (% dose): unmetabolized APAP: 2.43 (0.86) APAP-G: 12.8 (4.1) APAP-S: 47.6 (8.1)
	Comment: Total recovery ~ 63%; limited capability of neonates for glucuronidation (~1/4th of adults) but well developed sulfation (higher than adults)				
Neonate	3	Newborn (1-3 days)	10 mg/kg, oral	4.9 (0.9)[b]	Urinary G:S ratio = 0.34
Children	7	3-9 y		4.5 (0.6)[b]	Urinary G:S ratio = 0.75
	4	12 y		4.4 (0.7)[b]	Urinary G:S ratio = 1.61
Adults [53]	4	Adult (23-30y)		3.6 (0.1)[b]	Urinary G:S ratio = 1.80
	Comment: Total recovery ~ 70% infants, ~80% others; overall rate of elimination of acetaminophen was similar across age groups; age-related differences were observed in glucuronidation and sulfation; adult pattern of elimination was observed by age 12 years				

a: mean (sd); b: calculated from urine data

Key: APAP – acetaminophen, APAP-G acetaminophen glucuronide; APAP-S acetaminophen sulfate; G:S - glucuronide/sulfation metabolite ratio, T½ - elimination half-life

Acetaminophen-associated hepatotoxicity is dependent in part on two mechanisms working together: the generation of the reactive NAPQ1 metabolite intermediate, and depletion of glutathione (conjugates NAPQ1 and renders it harmless) and liver sulfur stores. The activity of CYP2E1, the enzyme responsible for generating NAPQ1 is thought to be reduced in neonates and may, in part, be responsible for reducing the incidence of hepatotoxicity in this age group. Moreover, in younger infants, a greater fraction of the administered acetaminophen dose is excreted unchanged in the urine versus adults.

4.5.2 Estimates for Threshold for Toxicity in Acute Overdose

Significantly, reports from the American Association of Poison Control Centers (AAPCC) indicate that, even though there are a large number of exposures to acetaminophen products in the pediatric population, hepatic injury is extremely unusual. Even accidental unsupervised pediatric ingestions of adult acetaminophen dosage forms infrequently produce hepatic injury, in part, because the dose actually absorbed is usually below the threshold for toxicity. In McNeil professional education materials for physicians, we state that in children, hepatic toxicity may occur following an acute accidental overdose of greater than 150 mg/kg. The most current view among medical toxicologists is that an acute

accidental overdose of greater than 200 mg/kg is thought to be the threshold for toxicity in children [54,55].

Anderson et al [56] retrospectively reviewed data from emergency department visits by 121 pediatric patients, ages 1 to 5 years, with accidental overdose of acetaminophen at doses of > 50 mg/kg and quantifiable acetaminophen concentrations at four hours post dose. The demographic and concentration data are summarized in Table 4-4.

Table 4-4 Demographic Summary from Accidental Acetaminophen Overdose Ingestion Study by Anderson et al [56]

N	121 patients
Mean (sd) age	33 (9) months
Mean (sd) weight	14.6 (2.8) kg
Median (range) ingested dose	165 (50-822) mg/kg
Median (range) concentration	30 (5.5-181) mg/L at 4 h

Despite the wide range of ingested doses, no acetaminophen toxicity was reported due to early interventions. Anderson et al developed a pharmacokinetic-pharmacodynamic model using these toxicology data, combined with literature data[5] and their research group's data [57] of acetaminophen pharmacokinetics to predict hepatotoxic doses and concentrations in children [56]. They developed the model to estimate doses that would simulate hepatotoxic plasma concentrations using two methods to account for body size in children: per kilogram weight normalization (standard) and allometric weight scaling of pharmacokinetic parameters (mechanistic basis).

Based on simulations in 1000 subjects, the simulated doses that resulted in the upper 95% confidence interval of peak concentrations below the toxic threshold of 200 mg/L[6] at four hours are listed in Table 4-5. The estimates obtained from the allometric-weight model are consistent with the estimates from medical toxicologists that the threshold for toxicity for an acute accidental overdose is greater than 200 mg/kg in children. The per kilogram weight model provided a higher estimate of threshold dose at 375 mg/kg for all ages above one year.

[5] Parameter estimates and their variability were obtained from Goodman LS, Gilman AG, Rall TW, Murad F, editors. The pharmacological basis of therapeutics. 7th Ed. NY: MacMillan Publishing Co; 1985: p1709

[6] From Rumack-Matthew nomogram

Table 4-5 Simulated (Predicted) Threshold Acetaminophen Doses That Result in Peak Concentration <200 µg/mL at 4 hours (Upper 95% CI) [56]

Age Group	Threshold Dose (mg/kg)	Total Acute Dose Ingested (g)
Allometric Weight Model		
1 year (8-12 kg or 17.6-26.4 lbs)	300	2.2 to 3.6
5 year (16-22 kg or 35.2-48.4 lbs)	280	4.9 to 6.2
Adult (55-85 kg or 121-187 lbs)	230	12.7 to 19.6
Per kilogram Weight Model All ages > 1 year	375	

A retrospective 10-year review [58] of children found that intentional and unintentional acetaminophen overdoses occurred with similar frequency, and that dosing errors with therapeutic intent was relatively uncommon, as was hepatocellular injury. Data from 322 patients (208 girls and 114 boys, aged 1-17 years) were obtained. Ingestions were intentional in 140 patients (median age, 14 years) and unintentional in 172 (median age, 2 years). Another 10 cases represented dosing errors with therapeutic intent (median age, 3.5 years).

The range of doses ingested was very wide for all patients (4 to 8333 mg/kg), but the median dose was comparable between the intentional and unintentional groups (172 vs 150 mg/kg/24h). Patients with dosing errors had a lower median dose (90 mg/kg/24h). Twenty-seven patients had hepatocellular injury, defined as serum aminotransferase levels > 2x upper reference range; of these, four had severe hepatotoxic effects and one died. Hepatocellular injury occurred in 10.0% of the dosing error group, 17.9% of the intentional group, and 0.6% of the unintentional group. No patients underwent liver transplantation.

Hepatocellular injury was associated with dose greater than 150 mg/kg (odds ratio [OR, 17.9; 95% confidence interval [CI], 2.3-139.2), presentation longer than 24 hours after ingestion (OR, 335.0; 95%CI, 40.8-275.0), age 10 to 17 years (OR, 36.9; 95% CI, 4.9-275.4), and intentional overdose (OR, 37.2; 95% CI, 5.0-278.2).

As discussed by the investigators [58], their study has four limitations inherent in a retrospective medical record–based survey:

- It relied on information recorded by multiple caregivers and patient self-report that may contain inaccuracies.
- Doses may be overestimated because common clinical practice is to estimate the dose ingested based on worst-case scenario in the younger age group when the dose is considered on a per-kilogram basis.
- Cases are representative of those with suspected acetaminophen intoxication seen at a specialized tertiary care institution, so data may be skewed to greater severity compared with a community hospital.
- The small number of cases with significant hepatocellular injury during the 10-year review period prohibited a multivariate analysis necessary to critically examine associations between risk factors and control for confounding. Without this type of analysis, it is not possible to identify independent risk factors.

4.5.3 Repeated Supratherapeutic Ingestions in the Pediatric Population

Repeated supratherapeutic overdose in pediatric patients has been described when parents or caregivers have repeatedly given substantially more than the maximum-labeled daily dose of acetaminophen. Most of these cases are unintentional and most serious cases involve parents administering adult products to children or incorrect doses to children under age two. McNeil has requested that FDA allow the dosing instructions for children under two years of age to be added to pediatric product labels. Further details about pediatric dosing and supporting pediatric pharmacokinetics and clinical efficacy data are described in Section 6 of this document.

In a prospectively designed study, Kozer et al [59] studied the metabolic status and liver function of children presenting at a pediatric emergency department or pediatric ambulatory care unit in Israel. Children, ages 2 months to 10 years, were divided into three groups based on whether or not they were febrile and had been treated with repeated doses of acetaminophen in the therapeutic (~75 mg/kg/day) or supratherapeutic range for more than 72 hours. Table 4-6 summarizes the statistically significant differences among the laboratory assessments of aspartate aminotransferase (AST), and reduced glutathione (GSH) and glutathione-S-transferase (GST) measured in erythrocytes). No differences were detected for alanine aminotransferase (ALT), gammaglutamyl transferase (GGT), alkaline phosphatase (ALP), and glutathione reductase (GR).

Table 4-6 Demographic Data of Children and Selected Laboratory Values Following Therapeutic and Supratherapeutic Repeat Doses [59]

Group[a]	N	Age years Mean ± sd	APAP Dose[b] mg/kg/day Mean ± sd (range)	Median AST IU/L	GSH (µmol/gHb) Mean ± sd	GST (U/min/gHb) Median
1 (afebrile controls)	24	6 ± 3	No treatment	29	5.68 ± 1.88 [c]	2.18 [c]
2 (fever therapeutic doses)	13	3.5 ± 2.6	50 ± 15 (30-75)[d]	28	4.43 ± 1.54 [c]	3.17
3 (fever supratherapeutic dose)	14	2.2 ± 1.8	107 ± 28 (80-180)[d]	55 [b]	2.27 ± 1.06 [c]	4.58 [c]

a: Patients were excluded from the study if they had known chronic liver disease, suspected viral hepatitis, or treatment with a potential hepatotoxic drug or drugs that induce cytochrome P450
b: Patients had received this dose for > 72 hours before t the emergency department or clinic visit.
c: statistically significant
d: Duration of dosing [3.9 ± 1.7 (3-9) days]
Abbreviations: AST: aspartate aminotransferase; GST: glutathione-S-transferase; GSH: reduced glutathione

A mild elevation in AST and reductions in erythrocyte GSH and GST were observed for the high dose group. Investigators noted the mechanism for the lower glutathione in erythrocytes is not clear, and hypothesized that it may be indirect evidence of depleted intrahepatic glutathione, but that this hypothesis should be further tested in future studies. They also summarize the limitations of their study [59]:

- Acetaminophen doses given to the children were calculated based upon the parent/caregiver's report, which depended on recall and was prone to reporting bias, so the possibility of over- or under-estimation of doses cannot be excluded.
- The methodology used in this study could not prove a causative effect of acetaminophen in decreasing erythrocyte glutathione content as other variables that were not controlled may have affected the outcome.

4.6 Reference List

1. Gelotte CK, Auiler JF, Lynch JM, et al. Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. Clin Pharmacol Ther 2007;81:840-848.
2. McNeil Consumer Healthcare Clinical Study Report for Protocol 11-005: Acetaminophen disposition at 4 g/day for 4 days in moderate hepatic-impaired and matched-control adults. Fort Washington, PA: McNeil Consumer Healthcare, 2007 (data on file).
3. Allegaert K, de Hoon J, Verbesselt R, et al. Intra- and interindividual variability of glucuronidation of paracetamol during repeated administration of propacetamol in neonates. Acta Pædiatrica, 2005; 94: 1273–1279.
4. Hendrix-Treacy S, Wallace SM, Hindmarsh KW, et al. The effect of acetaminophen administration on its disposition and body stores of sulfate. Eur J Clin Pharmacol 1986;30:273–278.
5. Hindmarsh KW, Mayers DJ, Wallace SM, et al. Increased serum sulfate concentrations in man due to environmental factors: Effects on acetaminophen metabolism. Vet Hum Toxicol 1991;33:441–445.
6. Schmid R. Hammaker L. Glucuronide formation in patients with constitutional hepatic dysfunction (Gilbert's Disease). New Eng J Med 1959;260:1310-1314.
7. Rumack BH. Acetaminophen toxicity: The first 35 years. J Toxicol Clin Toxicol 2002;40:3–20.
8. Court MH, Duan SX, Von Moltke LL, et al. Interindividual variability in acetaminophen glucuronidation by human liver microsomes: Identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. J Pharmacol Exp Ther 2001;299:998-1006.
9. Burchell B. Genetic variation of human udp-glucuronosyltransferase implications in disease and drug glucuronidation. Am J Pharmacogenomics 2003;3:37-52.
10. Reiter C. Weinshilboum R. Platelet phenol sulfotransferase activity: Correlation with sulfate conjugation of acetaminophen. Clin Pharmacol Ther 1982;32:612-621.
11. Pacifici GM. Inhibition of human liver and duodenum sulfotransferases by drugs and dietary chemicals: A review of the literature. Int J Clin Pharmacol Ther 2004;42:488-495.
12. Chen W, Luke L, Stella J, et al. Oxidation of acetaminophen to its toxic quinone imine and nontoxic catechol metabolites by baculovirus-expressed and purified human cytochromes P450 2E1 and 2A6. Chem. Res. Toxicol 1998;11:295–301.
13. Dahlin DC, Miwa GT, Lu AYH, et al. N-acetyl-p-benzoquinone imine: A cytochrome P450-mediated oxidation product of acetaminophen. Proc Natl Acad Sci USA 1984;81:1327–1331.
14. Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000;67:275–282.
15. Prescott LF. Paracetamol overdosage: Pharmacological considerations and clinical management. Drugs 1983;25:290-314.
16. Prescott LF. Drug conjugation in clinical toxicology. Biochem Soc Trans 1984:12:96-99.
17. Davis M, Simmons CJ, Harrison NG, et al. Paracetamol overdose in man: Relationship between pattern of urinary metabolites and severity of liver damage. Quarterly J Med New Series XLV 1976;178:181-191.
18. Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmacol 1980;10:291S-298S.
19. Slattery JT, Levy G. Acetaminophen kinetics in acutely poisoned patients. Clin Pharmacol Ther 1979;25:184-195.
20. Dart RC, Rumack BH. Acetaminophen (paracetamol). In: Dart RC, ed. Medical Toxicology 3rd edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2003:723–738.

21. Yang XX, Hu ZP, Chan SY, et al. Monitoring drug–protein interaction Clin Chimica Acta 2006;365:9– 29
22. Chitturi S, George J. Hepatotoxicity of commonly used drugs: nonsteroidal anti-inflammatory drugs, antihypertensives, antidiabetic agents, anticonvulsants, lipid-lowering agents, psychotropic drugs. Semin Liver Dis 2002;22:169– 83.
23. Davern TJ, James LP, Hinson JA, et al. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. Gastroenterol 2006;130:687–694.
24. James LP, Alonso EM, Hynan LS, et al. Detection of acetaminophen protein adducts in children with acute liver failure of indeterminate cause. Pediatrics 2006; 118; e676-e681.
25. James LP, McCullough SS, Lamps LW, et al. Effect of N-acetylcysteine on acetaminophen toxicity in mice: relationship to reactive nitrogen and cytokine formation. Toxicol Sci 2003; 75: 458-467.
26. Michael SL, Pumford NR, Mayeux PR, et al.. Pretreatment of mice with macrophage inactivators decreases acetaminophen hepatoxicity and the formation of reactive oxygen and nitrogen species. Hepatology 1999; 30: 186-195.
27. Bond GR. Acetaminophen protein adducts: A review Clin Toxicol 2009;47:2-7.
28. James LP, Simpson P, Rahman S, et al. Detection of acetaminophen protein adducts in serum during therapeutic dosing of acetaminophen in healthy volunteers. Hepatology 2007; 46 (suppl 1):812A
29. Mitchell JB, Jollow DJ, Potter WZ. Acetaminophen-induced hepatic necrosis: I. Role of drug metabolism. J Pharmacol Exp Therapeut 1973;187:185-194.
30. Lauterburg BH. Analgesics and glutathione. Am J Ther 2002;9:225-233.
31. Mitchell JR, Thorgeirsson SS, Potter WZ, et al. Acetaminophen-induced hepatic injury: Protective role of glutathione in man and rationale for therapy. Clin Pharmacol Ther 1974;16:676-684.
32. Stork CM, Rees S, Howland MA et al. Pharmacokinetics of extended relief versus regular release Tylenol in simulated human overdose. Clin Toxicol 1996;34:157-162.
33. Douglas DR, Sholar JB, Smilkstein MJ. A pharmacokinetic comparison of acetaminophen products (Tylenol Extended Relief vs Regular Tylenol). Acad Emerg Med 1996;3:740-744.
34. Rose SR, Gorman RL, Oderda GM, et al. Simulated acetaminophen overdose: Pharmacokinetics and effectiveness of activated charcoal. Ann Emerg Med 1991; 20:1064-1068.
35. Hassig SR, Linscheer WG, Murthy UK, et al. Effects of PEG-electrolyte (colyte) lavage on serum acetaminophen concentrations: A model for treatment of acetaminophen overdose. Dig Dis Sci 1993;38:1395-1401.
36. Vance MV, Selden BS, Clark RF. Optimal patient position for transport and initial management of toxic ingestions. Ann Emerg Med 1992;21:243-246.
37. Green R, Grierson R, Sitar DS, et al. How long after drug ingestion is activated charcoal still effective? Clinical Toxicology 2001;31:601-605.
38. Christophersen AB, Levin D, Hoegberg LC, et al. Activated charcoal alone or after gastric lavage: A simulated large paracetamol intoxication. Br J Clin Pharmacol 2002;53:312-317.
39. Lauterburg BH, Mitchell JR. Therapeutic doses of acetaminophen stimulate the turnover of cysteine and glutathione in man. J Hepatol 1987;4:206-211.
40. Burgunder JM, Lauterburg BH. Decreased production of glutathione in patients with cirrhosis. Eur J Clin Invest 1987;17:408-414.

41. Bianchi G, Bugianesi E, Ronchi M, et al. Glutathione kinetics in normal man and in patients with liver cirrhosis. J Hepatol 1997;26:606-613.
42. Braun L, Kardon T, Puskas´ F. Regulation of glucuronidation by glutathione redox state through the alteration of UDP-glucose supply originating from glycogen metabolism. Arc Biochem Biophys 1997;348:169-173.
43. Ganry H, Pruvot F, Vesque D, et al. Hepatic and Renal Safety of Paracetamol: 3 g or 4 g per day? La Presse Médicale 2000;30:724-730.
44. Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidem Drug Safety 2006;15:241-243.
45. FDA Working Group. Clinical White Paper, CDER/PhRMA/AASLD Conference, November 2000. Accessed May 21, 2009 at http://www.fda.gov/cder/livertox/clinical.pdf
46. Summary tables of studies on file at McNeil.
47. Temple AR, Lynch JM, Vena J, et al. Aminotransferase activities in healthy subjects receiving three-day dosing of 4, 6, or 8 grams per day of acetaminophen. Clin Toxicol 2007;45:36-44.
48. den Hertog HM, van der Worp HB, van Gemert HMA, et al. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. Lancet Neurol 2009; 8: 434–40
49. Daly FF, O'Malley GF, Heard K, et al. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. Ann Emerg Med 2004; 44:393–398.
50. Dargan PI, Jones AL. Accidental staggered paracetamol overdoses in the United Kingdom: Epidemiology and outcome. Clin Toxicol 2002;40:339 (abstract).
51. Rumack BH: Acetaminophen overdose in young children. Am J Dis Child 1984, 138:428–433.
52. Levy G, Khanna NN, Soda DM, et al. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and d-glucaric acid excretion. Pediatrics 1975;55:818-825.
53. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children, and adults. Clin Pharmacol Ther 1976;19:284-94.
54. Tenenbein M. Acetaminophen: The 150mg/kg Myth. Clin Toxicol 2004;42:145-148
55. Dart RC et al. Acetaminophen poisoning: An evidence-based consensus guideline for out-of-hospital management. Clin Toxicol 2006;44:1-18.
56. Anderson BJ, Holford NHG, Armishaw JC, Aicken R. Predicting concentrations in children presenting with acetaminophen overdose. J Pediatr 1999; 135: 290-295.
57. Anderson B, Holford N, Woollard G, Kanagasundarum S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. Anesthesiology 1999; 90: 411-21
58. Alander SW, Dowd D, Bratton SL, et al.: Pediatric acetaminophen overdose:risk factors associated with hepatocellular injury. Arch Pediatr Adolesc Med 2000, 154:346–350.
59. Kozer E, Evans S, Barr J, et al. Glutathione, glutathione-dependent enzymes and antioxidant status in erythrocytes from children treated with high-dose paracetamol. Br J Clin Pharmacol 2003; 55: 234-240.

SECTION 5 ESTIMATION OF THRESHOLD DOSE FOR ACETAMINOPHEN TOXICITY IN SUBGROUPS

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5 ESTIMATION OF THRESHOLD DOSE FOR ACETAMINOPHEN TOXICITY IN SUBGROUPS

5.1 Key Points

Chronic Alcohol Abusers

- Maximum daily therapeutic doses (4000 mg/day) of acetaminophen have been shown to be well tolerated by recently abstinent chronic alcohol abusers in a series of five prospective randomized controlled studies with increasing days of exposure.
- Metabolic suppositions rationalizing a lower threshold dose for hepatotoxicity in chronic alcoholics or individuals with preexisting liver disease (who are often chronic alcoholics with liver disease) are often cited without supportive prospective clinical data.
- The chronic alcoholic population has known behaviors, including greater risk of suicide, comorbid substance abuse, impaired judgment, and accidental deaths associated with risk-taking behaviors, that are likely associated with acetaminophen overdoses.
- Chronic alcohol use in association with acetaminophen overdose may be a risk factor for hepatotoxicity due to late presentation and delay in antidote treatment.

Pre-Existing Liver Disease

- New and published pharmacokinetic studies show that individuals with liver disease have a modest increase in the elimination half-life of acetaminophen (about 1 to 2 h on average) that does not lead to progressive accumulation of acetaminophen with repeat dosing.
- While body clearance is about 15% to 60% lower on average, which reflects slower acetaminophen removal, this is not relevant to the biotransformation to metabolites, which has been shown across multiple studies to be essentially the same as that in healthy adults.
- Importantly, new and published metabolism data in individuals with and without liver disease show that the amount of thiol metabolites (a surrogate marker of

NAPQI[1] formation) is similar, demonstrating no decrease in glutathione conjugation or increase in metabolism by CYP2E1 in individuals with liver disease.

- Acetaminophen metabolism by glucuronidation (a nontoxic metabolic pathway) increases with repeated 1000 mg doses up to 4000 mg/day for four days in individuals with diseased and healthy livers. Consecutive daily dosing induces glucuronidation, resulting in increased body clearance of acetaminophen and increased production of the glucuronide metabolite.

[1] NAPQI (N-acetyl-*p*-benzoquinoneimine) is a highly reactive intermediate, which is conjugated with glutathione to produce the inert, nontoxic thiol metabolites: cysteine, mercapturate, methylthioacetaminophen, and methanesulfinylacetaminophen.

5.2 Threshold Dose Estimates at the Center of Scientific Debate

Published case series report potential risk factors for acetaminophen hepatotoxicity, but those series that have originated in referral centers (eg, liver transplant units) [1,2] might be prone to selection and referral bias [3]. Two such potential risk factors include chronic alcohol abuse and preexisting liver disease, although these continue to remain highly controversial within the scientific and medical community [1,4,5,6,7,8]. This issue is important given the prevalence of alcoholism and given the adverse effects of alternative analgesics. Furthermore, estimation of threshold dose for acetaminophen hepatotoxicity in these two subgroups are confounded by metabolic suppositions, population risk-taking behaviors, and known limitations of spontaneous adverse event reporting, poison control databases, and overdose case report and case series data.

The databases and case series that FDA cites as support for threshold toxicity have acknowledged methodological weaknesses. Causality cannot be determined from these data, which do not contain a control group and likely contain biases, including referral and ascertainment bias. Assessments in FDA's Adverse Event Reporting System (AERS) are a collection of case reports, subject to underreporting, as well as underascertainment or overascertainment, and thereby are susceptible to artifacts [9]. From most of these case data, it is not possible to determine the true dose of acetaminophen ingested or the patient's true intent at the time acetaminophen may have been ingested. Moreover, these data cannot be used reliably to test hypotheses but rather to generate them [9,10], including the estimation of threshold dose in subgroups of individuals who consume or abuse alcohol and/or who have preexisting liver disease.

5.3 Threshold of Overdose Toxicity in Chronic Alcohol Users

5.3.1 Overview of Current Scientific Data and Unanswered Questions

In a recent independent review of acetaminophen overdose in *Drug Safety* [11], the authors conclude: "Hepatotoxicity has also been reported after therapeutic doses, but critical analysis indicates that most patients with alleged toxicity from therapeutic doses have taken overdoses." Two other factors related to less favorable outcomes for unintentional (not reported as suicide) acetaminophen overdoses are late presentation and delay or failure to receive the antidote, N-acetylcysteine (NAC). They have been suggested to play a role in outcomes observed in individuals using multiple acetaminophen-containing preparations or narcotic-containing preparations for chronic pain [3]. However, metabolic suppositions rationalizing a lower threshold dose for hepatotoxicity are often cited for chronic alcoholics

or individuals with preexisting liver disease (who are often chronic alcoholics with liver disease), even though the chronic alcoholic population has greater risks of completed suicide, comorbid substance abuse, slow death from cirrhosis of the liver, and accidental deaths associated to risk-taking behaviors [12].

Chronic alcohol use in association with acetaminophen *overdose* may be a risk factor for hepatotoxicity due to late presentation and delay in NAC treatment. Dr. Laurie Prescott, a distinguished investigator of acetaminophen (paracetamol) science and overdose, writes in his 2000 review [4] on paracetamol, alcohol, and the liver:

> Apart from the presence of underlying chronic liver disease in some patients, there is no difference in the clinical course of paracetamol poisoning in alcoholics. However, alcoholics may appear to be more susceptible to the hepatotoxicity of paracetamol because they often present late. Patients who present late are more severely poisoned and have a much worse prognosis than those who come to hospital early, regardless of alcohol intake [13,14,15,16]. In addition, the apparent association of severe liver damage and excessive alcohol intake largely reflects a population which is likely to take overdoses [15]. These are important sources of bias that exaggerate the belief that chronic alcoholics suffer more severe liver damage following an overdose of paracetamol.

There is no universally recognized or used definition of chronic alcoholism. The World Health Organization states that “alcoholic” is generally taken to refer to chronic continual drinking or periodic consumption of alcohol, which is characterized by impaired control over drinking, frequent episodes of intoxication, and preoccupation with alcohol and the use of alcohol despite adverse consequences [17]. Ali et al [18] point out that this subjective characterization of alcoholic makes it difficult to discern with certainty this risk-modifier in overdose patients, especially when published toxicology literature or poison control databases on acetaminophen overdose and toxicity are reviewed retrospectively.

In their review of the literature, Graham et al [11] describe two main reasons for concluding that alcohol does not potentiate the hepatotoxicity of acetaminophen sufficiently to make therapeutic doses hepatotoxic. Firstly, as with cases of hepatotoxicity ascribed to therapeutic doses of acetaminophen in nonalcohol drinking adults and children, extrapolation of the plasma concentrations in moderate and heavy alcohol drinkers with hepatotoxicity often indicates that excessive doses were consumed [19,20,21]. For those cases where plasma concentrations are low, the true dose cannot be ascertained because often the chronic alcoholic has also presented late. Secondly, all prospective studies to

date indicate that therapeutic doses of acetaminophen at 3900 to 4000 mg/day are not hepatotoxic in alcoholic subjects [22,23,24,25,26].

5.3.2 Pharmacokinetic/Metabolism Studies Do Not Suggest a Risk of Therapeutic Doses of Acetaminophen in Alcoholics

One side of the scientific debate favors suppositions of increased hepatotoxicity near therapeutic doses for chronic alcoholics or individuals with preexisting liver disease by citing early animal and human metabolism data of acetaminophen and ethanol as corroboration to published case reports. Alcohol competes with acetaminophen and is preferentially bound to cytochrome P450 2E1 (CYP2E1) when both are present, thus blocking the metabolism of acetaminophen to the toxic intermediate, NAPQI [27]. Available evidence from chlorzoxazone[2] metabolism data in nondrinking adults and alcohol abusers suggests that there is about a one-to-two day window after alcohol is removed from the blood when CYP2E1 activity is increased due to alcohol induction, and hence, available to produce more NAPQI [28,29].

In a study [30] of healthy adults examining the effect of alcohol induction on acetaminophen metabolism immediately after alcohol was cleared, the fraction of the acetaminophen dose converted to NAPQI, and indirectly measured as detoxified urinary thiols (cysteine and mercapturic conjugates), was modestly increased by 21.6% ($p < 0.03$). While supporting the operational mechanism, the increase from 7.5% to 9.2% in the fraction of dose excreted as total thiols is clinically insignificant, causing no additional risk of acetaminophen hepatotoxicity at therapeutic doses in adults who are moderate or occasional binge drinkers of alcoholic beverages.

Several clinical metabolism studies [31,32,33,34,35,36] have been conducted comparing the biotransformation of acetaminophen between nondrinking control subjects and chronic alcoholics after ceasing alcohol consumption. Overall, these studies show that there are no, or only fairly small, changes in thiols produced within the first few days after ceasing alcohol consumption. These data provide metabolic evidence that the effect of alcohol on acetaminophen oxidation by CYP2E1 induction is minimal, and that chronic alcoholics are not at risk of hepatotoxicity with therapeutic doses of acetaminophen

[2] A metabolic probe for assessing *in vivo* activity of the CYP2E1 enzyme.

5.3.3 Prospective Clinical Studies of 3900 and 4000 mg/day in Recently Abstinent Chronic Alcohol Abusers

Five prospective, randomized, double-blind, placebo-controlled studies have been completed in which maximum-labeled doses of acetaminophen were administered for up to five days to over 400 newly abstinent chronic alcoholics. Four of these studies were coordinated by the Rocky Mountain Poison and Drug Center (RMPDC) as part of a step-wise research program investigating the potential interaction of acetaminophen and alcohol in chronic alcoholics [23,24,25,26]. The fifth study was conducted by Bartels and colleagues in Canada and is similar in design to the studies conducted at RMPDC, except that the extended-release acetaminophen was administered, totaling 3.9 g/day for five days [22].

Hypothetically, if there is a potential risk of hepatic injury following therapeutic doses of acetaminophen, newly abstinent alcoholics would be the subpopulation of chronic alcoholics at greatest risk within the first two days of ceasing alcohol consumption. During this short period, CYP2E1 is maximally induced, and alcohol is not present to inhibit CYP2E1. As the length of alcohol abstinence increases, this hypothetical risk of hepatic injury would decrease, because CYP2E1 induction decreases with a half-life of 2.5 days following alcohol abstinence [28,29].

The safety findings of these five studies, which are outlined in Table 5-1, demonstrate that the maximum daily therapeutic dose of acetaminophen, 4000 mg/day, administered to newly abstinent chronic alcoholics does not result in hepatotoxicity, hepatic dysfunction, or hepatic failure. Across studies, there were no significant differences in mean aminotransferases (AST and ALT) or international normalized ratio (INR)[3] values between the acetaminophen and placebo groups following dosing with the current maximum-labeled daily. In addition, one study showed that continuous dosing of acetaminophen had no effect on plasma glutathione concentrations and another found no significant effect on alpha glutathione S-transferase levels [22]. Furthermore, no significant differences were detected between the acetaminophen and placebo groups in the number of subjects who developed an AST or ALT >200 IU/L. Multiple *post hoc* evaluations, including those of subjects with baseline elevations in ALT levels or AST/ALT ratios, those of subjects who were positive for hepatitis C antibody, and those of subjects who were malnourished,

[3] Laboratory test that measures the time for blood to clot and compares it to an average.

demonstrated no statistically significant differences between the acetaminophen and placebo groups in mean values for AST, ALT, or INR.

The safety findings were replicated across double-blind, randomized, placebo-controlled studies conducted by different investigators at detoxification sites in both the US and Canada. Importantly, these safety results are consistent with clinical acetaminophen metabolism data from several studies that compared the biotransformation of acetaminophen between nondrinking control subjects and chronic alcoholics after ceasing alcohol consumption [31-35]. The metabolism data show that there are no, or only fairly small, changes in thiols (surrogate marker for the NAPQI toxic intermediate) produced within the first few days after ceasing alcohol consumption, confirming that the effect of alcohol on acetaminophen oxidation by CYP2E1 induction is minimal. The metabolic rationale for hypothesizing increased risk of acetaminophen-induced hepatotoxicity at therapeutic doses in chronic alcoholics is not supported by clinical data.

A randomized, placebo-controlled trial evaluated the safety of maximum 4000 mg/day doses of acetaminophen for ten consecutive days in actively drinking adults with average alcohol consumption between one to three drinks per day [37]. Serum AST, ALT, bilirubin, and INR were measured at baseline, Day 4 and Day 11. Symptoms potentially related to liver injury were also recorded. At Day 4, no change from baseline values was detected for the acetaminophen and placebo groups, but the acetaminophen group had an increase in mean ALT at Day 11 of 8.7 IU／L. No subject developed symptoms of liver injury or met predefined criteria for hepatotoxicity or liver failure. The mild elevations of aminotransferase data from this study are consistent with data from acetaminophen studies in nondrinkers and non-alcoholics.

Table 5-1. Safety Findings of Clinical Studies of 3.9 and 4/g day in Recently Abstinent Chronic Alcohol Abusers

Study Design/ Population	Outcome measures	Treatment	N	Safety Findings
Pilot Two-Day [23] R, DB, PC, SC Alcoholic subjects entering a detoxification facility with a baseline AST and ALT ≤120 U/L and INR ≤1.5	ALT, AST, and INR were performed at baseline and repeated on Day 4. AST and INR also performed on Day 2	APAP 1 g q4h (4g/d) for 2 days Placebo Treatment initiated immediately after cessation of alcohol intake.	30 30	There were no statistically significant differences between groups in mean AST, ALT, or INR levels at any time. There were no statistically significant differences between groups with respect to frequency of AST, ALT, INR, BUN, or creatinine elevations.
Two-Day [24] R, DB, PC, SC Alcoholic subjects entering a detoxification facility with a baseline AST and ALT ≤120 U/L and INR ≤1.5	ALT, AST, and INR were performed at baseline and repeated on Days 2 and 4.	APAP 1 g q4h (4g/d) for 2 days Placebo Treatment initiated immediately after cessation of alcohol intake.	102 99	No statistically significant differences in AST, ALT, or INR levels after drug dosing were detected between groups. Number of subjects who developed an AST level above baseline: APAP-41 and placebo-42 (p=0.77). Number of subjects who developed an ALT level above baseline: APAP-52 and placebo-62 (p=0.12). Number of subjects who developed an INR level above baseline: APAP-52 and placebo-53 (p=0.78). Four subjects in the APAP group and 5 in the placebo group developed an AST or ALT level >120 U/L. No subject in either group developed an AST or ALT level >200 U/L. Post-hoc analysis found no increase in enzyme levels among subjects with a low body mass index or those judged as malnourished.

Table 5-1. (continued)

Study Design/ Population	Outcome measures	Treatment	N	Safety Findings
Three-Day [25] R, DB, PC, MC Alcoholic subjects entering a detoxification facility with a baseline AST and ALT ≤200 U/L and INR ≤1.5	ALT, AST, INR, and bilirubin were measured at baseline and repeated on days 2 to 5. In a subset of subjects plasma glutathione levels were measured at baseline and on day 3.	APAP 1 g q4h (4g/d) for 3 days Placebo Treatment initiated immediately following cessation of alcohol intake.	258 114	No statistically significant differences were detected between groups in mean ALT or AST levels at baseline or at any time after drug administration. Mean serum ALT on day 5: APAP-57 and placebo-55 (p=-0.706). ALT stayed the same or decreased in 32% of APAP and 28% of placebo subjects. Number of subjects who developed an ALT level greater than 3 times normal: APAP-19 (7.4%) and placebo-8 (7.0%). Number of subjects who developed an ALT >200 IU/L: APAP-8 and placebo-2. No significant change in mean INR or total bilirubin between the study groups throughout the study (p>0.05). In the subset of subjects in whom plasma glutathione levels were measured, there were no significant differences between groups; glutathione levels increased in both groups. Neither body mass index nor any degree of malnutrition correlated with increases in ALT.
Five-Day [26] R, DB, PC, MC Alcoholic patients entering a detoxification facility with a baseline AST and ALT ≤200 U/L and INR ≤1.5	ALT, AST, and INR were performed at baseline and repeated on days 2, 4, 6, and 7.	APAP 1 g q4h (4g/d) for 5 days Placebo Treatment initiated immediately following cessation of alcohol intake.	74 68	Mean serum ALT activity increased from 48 IU/L (95% CI 40, 57) to 62 IU/L (95% CI 49, 74) in the acetaminophen group and from 47 IU/L (95% CI 39, 55) to 49 IU/L (95% CI 39, 60) in the placebo group. Although ALT was not statistically different between the acetaminophen and placebo groups throughout the study, the ALT increase was statistically significant within the acetaminophen group (p<0.001). The highest ALT recorded was 238 IU/L in the acetaminophen group and 249 IU/L in the placebo group. The proportion of subjects that exceeded 3 X ULN on day 6 was 9% in the acetaminophen group and 5% in the placebo group. Mean INR remained within the normal reference range throughout the study in both groups.

Table 5-1. (continued)

Study Design/ Population	Outcome measures	Treatment	N	Safety Findings
Four-Day [22] R, TB, PC, SC Chronic alcohol abusers who had discontinued alcohol consumption 12-72 hours prior to enrollment and had a baseline AST and ALT ≤120 U/L and INR ≤1.5	ALT, AST, INR, and α-GST were performed at baseline and repeated daily for 5 days.	APAP Sustained release 1.3 g q8h x 11 doses Placebo Initiated within 12 to 27 hours following cessation of alcohol intake.	23 22	There were no statistically significant differences between groups in α-GST, AST, ALT, or INR after drug dosing. Relative change in α-GST was 46% vs 29% (p=0.5). Relative change in AST was –3% versus -6% (p=0.8).

Abbreviations: α-GST= α-gluathione-*S*-transferase, APAP=acetaminophen, ALT – alanine aminotransferase; AST – aspartate aminotransferase; DB=double-blind, INR – international normalized ratio; PC=placebo controlled, MC=multi-center, R=randomized, SC=single-center, TB=triple blind.

5.3.4 Other Confounding Behaviors to the Estimations of Threshold Doses

Alcohol use was reported in 57% of the cases and alcohol abuse was reported in 19% of the case series from the ALFSG [38]. Alcohol use was reported in 61-87% and 41% of the cases from the University of Pennsylvania Hospital series and from the AERS database, respectively. These percentages are consistent with reports in the medical literature with respect to patients presenting with any type of injury, including drug overdose, in association with alcohol use [39,40,41].

Alcohol use is a risk factor for increased injury severity and is associated with fatal injuries [39]. Alcohol use is a characteristic of 40% to 60% of motor vehicle accident victims, 32% to 46% of homicide victims, 20% to 50% of suicide victims, 25% to 50% of drowning victims and 40% to 64% of fire and burn victims [39,42 ,43,44]. Alcohol use has also been reported in 30% to 50% or more of drug overdose deaths not specifically attributable to acetaminophen [45]. Presenting to an emergency department with alcohol intoxication is a potential independent risk factor for premature death [46].

Alcohol use can negatively affect decision-making, impair judgment and memory, and decrease risk perception [47]. The association of alcohol and acetaminophen-induced injury, such as acute liver failure, may be related to risky behaviors that lead to acetaminophen overdose such as not reading and following acetaminophen dosing instructions, taking more than the recommended dose, and not getting quick medical attention following an acetaminophen overdose. These behaviors confound the estimation of true threshold doses for toxicity.

5.4 Threshold of Overdose Toxicity in Pre-Existing Liver Disease

5.4.1 Distinguishing Between Drug Clearance and Metabolism Data

Most published studies describe the pharmacokinetics of acetaminophen from plasma data alone, which is not informative with regard to the effect of liver disease on the biotransformation of acetaminophen. Pharmacokinetic parameters, such as elimination half-life (t½) and body clearance (CL/F), depict time-dependent changes in plasma concentrations of the pharmacologically active analgesic (acetaminophen itself) and provide no data on the formation or disposition of the toxic intermediate, NAPQI. Instead, the question of whether the diseased liver can adequately detoxify therapeutic doses of

acetaminophen can be addressed by measuring the fractional amounts of metabolites produced. Because cytochrome P4502E1 (CYP2E1) and hepatic glutathione contribute to the formation and detoxification, respectively, of NAPQI from acetaminophen, the effect of liver disease on both are relevant to the characterization of liver safety. Generally, the production of thiol metabolites are evaluated as a surrogate marker for the amount of NAPQI formed.

About 60 children and 362 adults with a wide variety of liver diseases, including various types of cirrhosis, hepatitis, nodular transformation, congenital hepatic fibrosis, and α_1-antitrypsin deficiency have been evaluated in 22 pharmacokinetic and/or metabolism studies published from 1961 through 2006. Additionally, there are two published repeat-dose pharmacokinetic studies in hepatic-impaired adults, and a recent repeat-dose metabolism study sponsored by McNeil [48] that produced new data in this liver-impaired population. In the latter study, subjects had diagnoses of hepatocellular cirrhosis secondary to hepatitis C and/or previous alcohol abuse, and they had a Child-Pugh score of 7 to 9, indicating moderate liver impairment. Of the 12 subjects completed, ten had chronic hepatitis C, and eight had been chronic alcohol abusers. An additional 13 control subjects without liver disease completed the study, and they were matched for age, weight, gender, race/ethnicity, and smoking status.

5.4.2 Single-Dose Acetaminophen Metabolism by Healthy and Diseased Livers is Similar

The data of utmost importance to gauge the metabolism of acetaminophen in liver disease are the fractional amounts of metabolite excreted in urine. Detailed biotransformation data of acetaminophen from single doses are available from McNeil Study 11-005 [48] and four published studies [33,49,50,51], and they are summarized in Table 5-2. Overall, mean (± sd) percents of unchanged acetaminophen and the glucuronide, sulfate, and oxidative thiol metabolites (sum of cysteine and mercapturate) were similar between healthy control and hepatic-impaired groups across studies. Within studies, no statistical differences were detected in means for any metabolite between the healthy control and hepatic-impaired groups. In McNeil Study 11-005 [48], a one-way analysis of variance detected no statistical differences in mean percents of unchanged acetaminophen and all metabolites. These data show that acetaminophen biotransformation by the diseased liver is similar to that by healthy livers after a single dose, a finding replicated across five studies.

Table 5-2 Urine Excretion Pattern of Acetaminophen and Metabolites from a Single Dose, Reported as Mean (±sd) Percent[a]

Study	Sample Size	Acetaminophen	Glucuronide	Sulfate	Thiols[b]	Total Recovered
McNeil 2007 [48][c]						
Control Subjects	11[d]	2.4 ± 0.8	49.0 ± 7.43	22.4 ± 7.0	5.5 ± 2.1	82.4 ± 14.1
Mild/Mod Liver Disease	12	2.9 ± 2.0	40.2 ± 13.3	27.4 ± 12.0	6.8 ± 2.5	79.0 ± 7.6
Zapater 2004 [51]						
Control Subjects	7	1.2 ± 0.6	59.9 ± 4.2	27.9 ± 4.4	9.7 ± 2.2	NR
Mild/Mod Liver Disease	9	1.6 ± 1.2	57.1 ± 7.6	30.4 ± 7.1	9.0 ± 2.8	NR
Severe Liver Disease	5	1.0 ± 0.5	53.5 ± 7.4	35.4 ± 7.9	9.2 ± 4.4	NR
Leung 1989 [50]						
Hepatitis B Cirrhosis	29	5 ± 2	58 ± 9	28 ± 7	9[e]	NR
Alcoholic Cirrhosis	13	3 ± 1	62 ± 9	27 ± 10	8[e]	NR
Villeneuve 1983 [33]						
Control Subjects	6	4.8 ± 0.7	57.3 ± 2.9	33.3 ± 3.3	4.6[e]	88.6 ± 3.4
Cirrhosis	11	5.0 ± 0.5	51.7 ± 3.3	37.1 ± 2.6	6.0[e]	73.9 ± 4.8
Forrest 1979 [49]						
Control Subjects	8	3.7 ± 0.2	54 ± 1.4	33 ± 1.2	8.6[e]	92 ± 0.6
Mild Liver Disease	8	2.7 ± 0.3	59 ± 2.3	29 ± 1.9	8.7[e]	81 ± 3.1
Severe Liver Disease	7	4.6 ± 0.8	50 ± 3.7	35 ± 3.1	8.4[e]	84 ± 5.5

a: Data are reported as percent of acetaminophen dose recovered [48,49,51] or as percent of total acetaminophen and metabolites recovered [33,50].

b: Thiols are the sum of cysteine and mercapturate metabolites.

c: Catechols were also measured in McNeil Study 11-005: 3.1 ± 2.6 and 2.4 ± 0.9 for control and hepatic-impaired subjects, respectively.

d: Urine data for two matched-control subjects were not available due to an error at the clinical site. Note that an additional matched-control had been enrolled due to uncertainty that the full set of subjects matching the hepatic-impaired subjects would be complete.

e: Mean data for cysteine and mercapturate metabolites were reported separately in the publication, but are summed here.

Abbreviations: sd – standard deviation, NR – not reported

5.4.3 New Comparative Data for Repeat-Dose Acetaminophen Metabolism in Adults with Pre-Existing Liver Disease

McNeil Study 11-005 [48] is the only study in adults with pre-existing liver disease that evaluated acetaminophen metabolism after repeat dosing of 1000 mg every six hours for four days, totaling 17 g. The duration of four days of dosing was chosen based on (i) estimates of half-lives for the metabolites in the liver-impaired subjects to project the time to reach steady-state pharmacokinetics, and (ii) the total number of days that the liver-impaired subjects would be housed in the clinic during the study.

Time-dependent changes in acetaminophen metabolism from the first dose to steady-state doses are shown in Table 5-3. For the matched-control subjects, the amount of glucuronide metabolite increased whereas the amount of sulfate metabolite decreased with repeat dosing. These differences are statistically significant, and consistent with changes reported in a disposition study of young healthy adults with repeat acetaminophen dosing of 1000, 1500, and 2000 mg every six hours [52]. The latter study reported increases in glucuronide formation that more than offset decreases in sulfate conjugation over time. Although the data suggest cofactor depletion with possible saturation of the sulfate pathway, increases in glucuronide produced with repeat dosing were more pronounced, indicating induction of glucuronosyltransferase, presumably UGT1A6 [52]. Enhanced glucuronidation with repeat dosing of acetaminophen is discussed in more detail in Section 4 of this document.

Similarly for the hepatic-impaired subjects, the amount of glucuronide metabolite increased and the amount of sulfate metabolite decreased with repeat dosing, and these differences are statistically significant [48]. The amount of acetaminophen excreted unchanged in the urine was statistically higher after repeat dosing, which is consistent with more acetaminophen being cleared directly by renal elimination.

An important finding is that there were no changes in the amount of thiol metabolites formed in either group with repeat dosing, as they are nearly identical after several grams of acetaminophen exposure. Total thiols are a surrogate marker for the amount of toxic intermediate, NAPQI, that is produced. Enhanced glucuronidation and increased renal excretion of unchanged acetaminophen in the hepatic-impaired group show biotransformation that is favorable with repeat therapeutic dosing at the maximum daily dose (4000 mg/d).

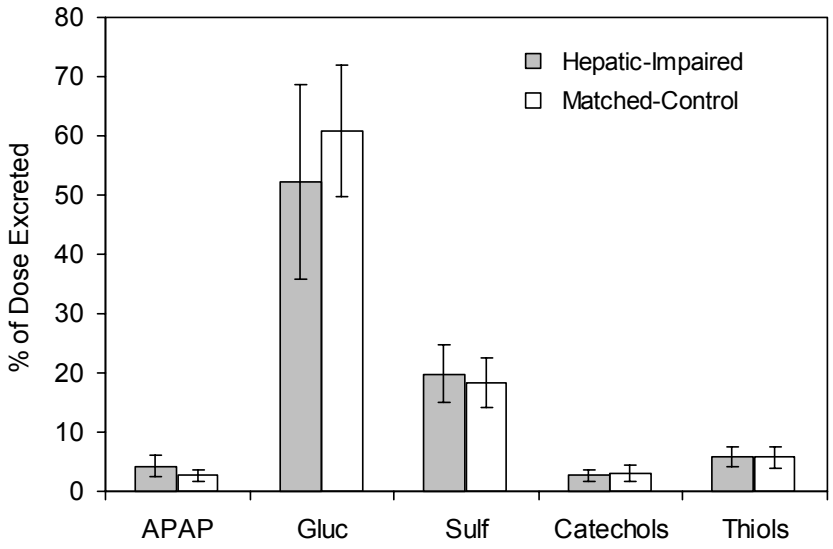
Table 5-3 Comparison by Dose of Mean (± sd) Percent Acetaminophen or Metabolite Excreted Within Study Group

	Hepatic-Impaired (n=12)			Matched-Control (n=11)		
	First Dose	**Last Dose**	**p-value[a]**	**First Dose**	**Last Dose**	**p-value[a]**
Acetaminophen	2.90 ± 0.1.99[b]	4.72 ± 1.66[b]	0.001	2.40 ± 1.78	2.53 ± 1.06	ns
Glucuronide	40.2 ± 13.3	52.1 ± 16.4	0.0001	49.0 ± 7.42	59.9 ± 11.7	0.008
Sulfate	27.4 ± 12.0	19.8 ± 4.94	0.016	22.4 ± 6.98	17.9 ± 4.16	0.01
Total Catechols[c]	2.44 ± 0.90[d]	2.91 ± 0.77[d]	0.038	3.09 ± 2.61	2.62 ± 0.72	ns
Total Thiols[e]	6.84 ± 2.47	5.77 ± 1.73	ns	5.51 ± 2.08	5.74 ± 1.86	ns

a: p-value from matched-pair t-test
b: n=10 subjects
c: The sum of methoxyacetaminophen (MO)-glucuronide and methoxyacetaminophen (MO)-sulfate
d: n=11 subjects
e: The sum of cysteine and mercapturate
ns – not significant

Figure 5-1 shows the urinary excretion pattern of acetaminophen and its metabolites excreted in urine as the percent of acetaminophen dose at steady state. Comparison of means between study groups using a one-way analysis of variance detected no statistical differences in the metabolites, indicating that the biotransformation of acetaminophen by the diseased liver is not different than the healthy liver. The percent of unchanged acetaminophen excreted is greater in the hepatic-impaired group, 4.26 ± 1.88% (n=12) versus 2.64 ± 1.09 (n=13) at p = 0.014, as this difference reflects higher renal elimination in the hepatic-impaired adults with repeat acetaminophen dosing.

Figure 5-1 Comparison of the Urinary Excretion Pattern of Acetaminophen and Its Metabolites by Study Group



5.4.4 Prospective Clinical Studies of 3000 to 4000 mg/day in Pre-Existing Liver Disease

The therapeutic use of acetaminophen in patients with liver disease has been reviewed recently [53]. In this section, the safety and tolerability of therapeutic doses of acetaminophen from five prospective clinical studies in 77 adults with liver disease of varying severity and etiology are highlighted. Repeated acetaminophen dosing at 4000 mg/day was studied for four, five, and 13 days in adults with chronic liver disease [48,54]. Repeated doses of 4000 mg/day for five days were also assessed in a placebo-controlled study of chronic alcohol abusers who were reactive for the hepatitis C virus

(HCV) antibody [26]. In addition, two clinical studies assessed 3000 mg/day in adults with cirrhosis for five days [55] and in adults with chronic hepatitis C infection for seven days [56]. The cumulative doses ranged from 15 to 56 g acetaminophen across studies. The key clinical findings are summarized in Table 5-4, and overall they show that multiple therapeutic doses of acetaminophen over several days were well tolerated. There were no increases in liver function tests including ALT, INR, bilirubin, no changes in viral load in adults with hepatitis, and no hepatic-related clinical adverse events.

Table 5-4 Summary of Clinical Outcomes for Therapeutic Acetaminophen Use in Adults with Liver Disease

	Benson [a] 1983 [54]	**Benson 1983 [54]**	**McNeil 2007 [48]**	**Andreasen 1979 [55]**	**Green 2005 [26]**	**Dargère 2000 [56]**
Population Evaluated						
Alcoholic Cirrhosis	–	2	2	4	–	–
Alcoholic / Hep C	–	–	6	–	18	–
Hep C Cirrhosis	–	3	4	–	–	–
Hepatitis C	–	7	–	–	–	17
Other [b]	6	8	–	–	–	–
Total (N)	6	20	12	4	18	17
Dosing Regimen	4g x 5d	4g x 14d	4g x 4d [c]	3g x 5d	4g x 5d	3g x 7d
Cumulative Exposure	20 g	56 g	17 g	15 g	20 g	21 g
Number Exposed	6	20	12	4	18	17
Clinical Outcomes	+	+	+	+	+	+
Change in ALT	↔	↔	↔	↔	↔	↔
Change in INR	NR	NR	NR	NR	↔	NR
Change in Other Labs [d]	↔	↔	↔	↔	NR	NR
Hepatic AEs [e]	None	None	None	None	None	None

a: Pilot study
b: Other includes Laennec's cirrhosis, cirrhosis (type unspecified), and primary biliary cirrhosis
c: One additional dose given on the morning of the fifth day.
d: Clinical laboratory tests associated with liver function.
e: Other clinically significant adverse hepatic events beyond changes in INR and laboratory tests.
Key: AEs – adverse events; ALT – alanine aminotransferase; INR – international normalized ratio; NR – not reported; NA – not applicable

5.5 Reference List

1. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-1372.
2. Makin AJ, Wendon J, Williams R. A 7 year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterology 1995;109:1907-1916.
3. Myers RP, Shaheen AA, Li B, et al. Impact of liver disease, alcohol abuse, and unintentional ingestions on the outcomes of acetaminophen overdose. Clin Gastroenter Hepatol 2008;6:918-925.
4. Prescott LF. Paracetamol, alcohol, and the liver. Br J Clin Pharmacol 2000;49:291-301.
5. Schmidt LE, Dalhoff K, Poulsen HE. Acute versus chronic alcohol consumption in acetaminophen-induced hepatotoxicity. Hepatology 2002;35:876-882.
6. Schiodt PV, Lee WM, Bondesen S, et al. Influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose. Aliment Pharmacol Ther 2002;16:707-715.
7. Ayonrinde OT, Phelps GJ, Hurley JC, et al. Paracetamol overdose and hepatotoxicity at a regional Australian hospital: a 4-year experience. Intern Med J 2005;35:655-660.
8. Prescott LF. Therapeutic misadventure with paracetamol: fact or fiction. Am J Ther 2000;7: 99-114.
9. Strom BL. How the US drug safety system should be changed. JAMA 2006;295:2072-2075.
10. Hennessy S. Disproportionality analyses of spontaneous reports. Pharmacoepidem Drug Safety 2004;13:503–504.
11. Graham GG, Scott KF, Day RO. Tolerability of paracetamol. Drug Safety 2005;28:227-240.
12. Tousignant M. Alcohol and drug use, suicide influences and factors. 2007. Advameg, Inc. Available at: http://www.deathreference.com/Sh-Sy/Suicide-Influences-and-Factors.html Accessed May 12, 2009.
13. Read RB, Tredger JM, Williams R. Analysis of factors responsible for continuing mortality after paracetamol overdose. Hum Toxicol 1986;5:201-206.
14. Brotodihardjo AE, Batey RG, Farrell GC, et al. Hepatotoxicity from paracetamol self-poisoning in western Sydney: a continuing challenge. Med J Aust 1992;157:382-385.
15. Makin AJ, Wendon J, Williams R. A seven-year experience of severe acetaminophen-induced hepatotoxicity (1987-93). Gastroenterology 1995;109:1907-1916.
16. Bradley MP, Nguyen-Van-Tam JS, Pearson JCG. `Late presenter' after paracetamol self-poisoning. J Epidemiol Community Health 1998;52:762-763.
17. WHO 2005. Lexicon of alcohol and drug terms published by the World Health Organization. World Health Organization Web Site. Available at: http://www.who.int/substance_abuse/terminology/who_lexiocn/en/ Accessed May 18, 2009.
18. Ali FM, Boyer EW, Bird SB. Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics. Alcohol 2008;42:213-218.
19. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol 2002;40:3-20.

20. Dart RC, Kuffner EK, Rumack BH. Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: a systematic review. Am J Ther 2000;7:123-134.
21. Prescott LF. Paracetamol, alcohol and the liver. Br J Clin Pharmacol 2000;49:291-301.
22. Bartles S, Sivilotti M, Crosby D, et al. Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial. Clin Toxicol 2008;46: 243–249.
23. Kuffner EK, Bogdan GM, Dart RC. Evaluation of hepatotoxicity in alcoholics from therapeutic dosing of acetaminophen. J Toxicol 1997;35:561(abstract)
24. Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminohpen on the liver of alcoholic patients. A randomized, double-blind, placebo-controlled trial. Arch Intern Med 2001;161:2247-2252.
25. Kuffner EK, Green JL, Bogdan GM, et al. The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in alcoholic patients – a multicenter randomized study BMC Medicine 2007; 5:13.
26. Green JL, Kuffner EK, Bogdan GM. Hepatic function in alcoholics throughout 5 days of maximal therapeutic dosing of acetaminophen (APAP) (abstract). Clin Toxicol 2005;43:683.
27. Slattery JT, Nelson SD, Thummel KE. The complex interaction between ethanol and acetaminophen. Clin Pharmacol Ther 1996;60:241-246.
28. Lucas D, Menez C, Girre C. Decrease in cytochrome P4502E1 as assessed by the rate of chlorzoxazone hydroxylation in alcoholics during the withdrawal phase. Alcohol Clin Exp Res 1995;19:362-366
29. Oneta CM, Lieber CS, Li J, et al. Dynamics of cytochrome P450E1 activity in man: Induction by ethanol and disappearance during withdrawal phase. J Hepatol 2002;36:47-52
30. Thummel KE, Slattery JT, Ro H, et al. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. Clin Pharmacol Ther 2000;67:591-599.
31. Lauterburg BH, Velez ME. Glutathione deficiency in alcoholics: risk factor for paracetamol hepatotoxicity. Gut 1988;29:1153-1157
32. Critchley JAJH, Cregeen RJ, Balali-mood M, Pentland B, Prescott LF. Paracetamol metabolism in heavy drinkers. Preceedings Brit Pharm Soc. 1982;13:276P-277P.
33. Villeneuve JP, Raymond G, Bruneau J, Colpron L, Pomier-Layrargues G. Pharmacokinetics and metabolism of acetaminophen in normal, alcoholic, and cirrhotic subjects. Gastroenterol Clin Biol. 1983;7:898-902
34. Skinner MH, Matano R, Hazle W, Blaschke TF. Acetaminophen metabolism in recovering alcoholics. Meth Find Exp Clin Pharmacol 1990;12:513-515.
35. Critchley JAJH, Lau GNS, Leung NWY. Paracetamol metabolism in Chinese alcoholics. Hepatol 1990;12:398 (Abstract).
36. Chern I, Brent J, Slattery J, Ritvo J, Kalhorn T, *et al*. Is it safe to give acetaminophen to alcoholics? A metabolic study. Vet Human Toxicol 1993;35:36 (Abstract)
37. Heard K, Green JL, Bailey JE, Bogdan GM, Dart RC. A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol. Aliment Pharmacol Ther. 2007;26:283-290
38. NDAC meeting September 19-20, 2002 transcript, http://www.fda.gov/ohrms/dockets/ac/02/trascripts/3882T1.htm and slides, http://www.fda.gov/ohrms/dockets/ac/02/slides/3882S1_04_Lee_files/frame.htm).

39. Chen LH, Baker SP, Guohua L. Drinking history and risk of fatal injury: comparison among specific injury causes. Accid Anal Prev 2005;37:245-251.
40. MacDonald S, Cherpitel CJ, DeSouza A, et al. Variations of alcohol impairment in different types, causes and contexts of injuries: Results of emergency room studies from 16 countries. Accident Anal Prevent 2006;38:1107-1112.
41. Anda RF, Williamson DF, Remington PL. Alcohol and fatal injuries among US adults-findings from the NHANES I epidemiologic follow-up study. JAMA 1988;260:2529-2532.
42. Pirkola SP, Isometsä ET, Heikkinen ME, et al. Suicides of alcohol misusers and non-misusers in a nationwide population. Alcohol Alcoholism 2000;35:70-75
43. Guohua Li, Smith G, Baker SP. Drinking behavior in relation to cause of death among US adults. Am J Pub Health 1994;84:1402-1406.
44. McLeod R, Stockwell T, Rooney R, et al. The influence of extrinsic and intrinsic risk factors on the probability of sustaining an injury. Accident Anal Prev 2003;35:71-80.
45. Coffin PO, Galea S, Ahern J, et al. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in NYC, 1990-1998 Addiction. 2003;98:739-747.
46. Davidson P, Koziol-McLain J, Harrison L, et al. Intoxicated ED patients: A 5-year follow-up of morbidity and mortality. Ann Emerg Med 1997;30:593-597.
47. George S, Rogers RD, Duka T. The acute effect of alcohol on decision making in social drinkers. Psychopharmacology 2005;182:160-169.
48. McNeil Clinical Study Report for 11-005: Acetaminophen disposition at 4 g/d for 4 days in moderate hepatic-impaired and matched-control adults. Fort Washington, PA: McNeil Consumer Healthcare, 2007 (data on file).
49. Forrest JA, Adriaenssens P, Finlayson ND, et al. Paracetamol metabolism in chronic liver disease. Eur J Clin Pharmacol. 1979;15:427-431.
50. Leung NWY, Chan TYK, Angkatavanich J, et al. Paracetamol metabolism in chinese patients with liver disease. Asia Pacific J Pharmacol 1990;5:9 (abstract).
51. Zapater P, Lasso De La Vega MC, Horga JF, et al. Pharmacokinetic variations of acetaminophen according to liver dysfunction and portal hypertension status. Ailment Pharmacol Ther 2004;20:29-36.
52. Gelotte CK, Auiler JF, Lynch JM, et al. Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. Clin Pharmacol Ther 2007;81:840-848.
53. Benson GD, Koff RS, Tolman KG. The therapeutic use of acetaminophen in patients with liver disease. Am J Ther 2005;12:133-141.
54. Benson GD. Acetaminophen in chronic liver disease. Clin Pharmacol Ther. 1983;33:95-101.
55. Andreasen PB, Hutters L. Paracetamol (acetaminophen) clearance in patients with cirrhosis of the liver. Acta Med Scand 1979; Suppl 624:99-105.
56. Dargère S, Colliet T, Crampon D, et al. Lack of toxicity of acetaminophen in patients with chronic hepatitis C: A randomized controlled trial. Gastroenterol 2000;118:A947 (abstract).

SECTION 6 ACETAMINOPHEN USE AND DOSING INSTRUCTIONS IN CHILDREN < 2 YEARS OF AGE

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6 ACETAMINOPHEN USE AND DOSING INSTRUCTIONS IN CHILDREN < 2 YEARS OF AGE

6.1 Overview

Acetaminophen is a safe and effective antipyretic and analgesic for the treatment of fever and mild to moderate pain in children and infants. Acetaminophen has been marketed in OTC formulations since 1959. Health care professionals routinely recommend acetaminophen to patients and consumers for use in children and infants. A considerable body of literature (published studies and unpublished clinical trial data) supports the continued use of acetaminophen these pediatric populations.

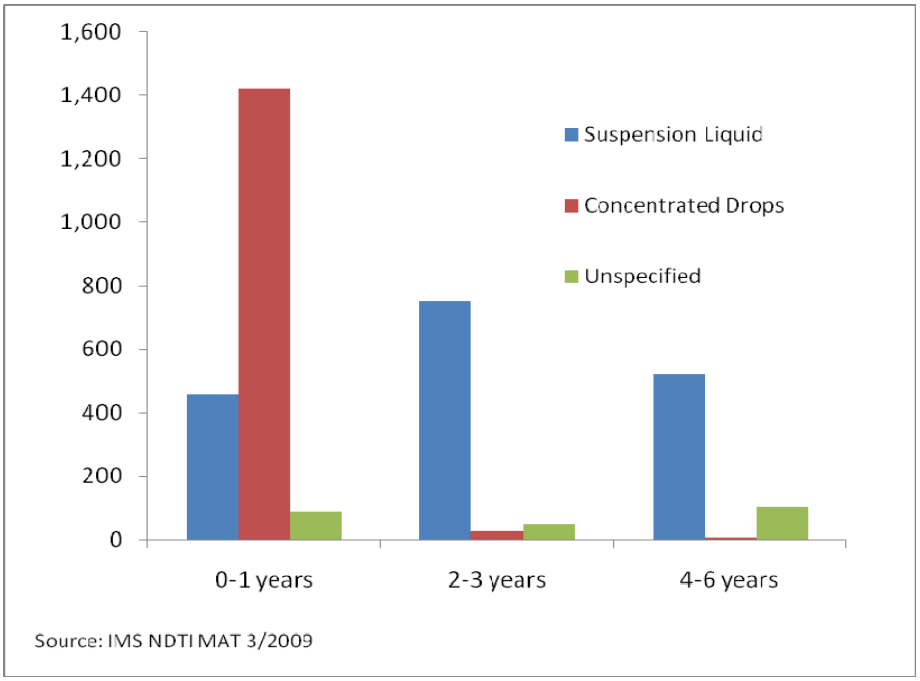
6.2 Key Points

- There is a medical and consumer need for acetaminophen pediatric products for children under the age of 2 years as evidenced by the volume of calls received by the McNeil Consumer Healthcare Consumer Care Call Center, where a majority of the calls (68%) were for children < 2 years. In contrast, the calls for Children's Motrin with labeling for children down to 6 months of age were evenly distributed across age groups
- Currently marketed products provide a range of options to consumers, including concentrated drops that are preferred by parents and caregivers of children who do not like medicines and may spit the dose out or fussy or sick children with difficulty swallowing larger amounts of drug.
- Considerable published literature and unpublished data from well-controlled clinical trials demonstrate the efficacy and safety of pediatric acetaminophen dosing for the management of fever and mild to moderate pain in children < 2 years of age.
- Many single- and multiple-dose pharmacokinetic and metabolism studies support the doses and dosing regimens proposed for use, through quantitative analysis of pharmacokinetic (and pharmacodynamic, efficacy, or safety) data.
- Incorporating dosing instructions for children 6 months to < 2 years of age targets a root cause of medication errors in this age population including administering greater than the labeled dose and administering concentrated pediatric drops (80 mg/0.8 mL) at the dose of the children's suspension liquid (32 mg/mL).

6.3 Medical Need for Pediatric Medicines in Children 6 months to < 2 Years of Age

Acetaminophen is used for symptomatic treatment of pain and fever in children under the age of two years. According to the American Academy of Pediatrics (AAP), most children will experience eight to ten colds in the first two years of life [1]. Acetaminophen is recommended for the treatment of fever associated with a cold by AAP and for use in relieving pain in children with Otitis Media by both AAP and the American Academy of Family Physicians [2]. Figure 6-1 summarizes the recommendations of acetaminophen by pediatricians over the past year by age group. The concentrated pediatric drops were mainly recommended for children between the ages of birth and 1 year.

Figure 6-1 Pediatrician Recommendations for Tylenol Liquid/Drops by Age



6.4 Labeling of Acetaminophen Products with Dosing Instructions for Children < 2 Years of Age Will Provide Important Information to Consumers

To decrease a preventable root cause of acetaminophen dosing errors, as discussed in Section 8.5.3, and decrease consumer confusion, dosing instruction for children 6 months to < 2 years of age should be included on the label of pediatric concentrated

acetaminophen containing products. Similar labeling on products containing ibuprofen is currently available.

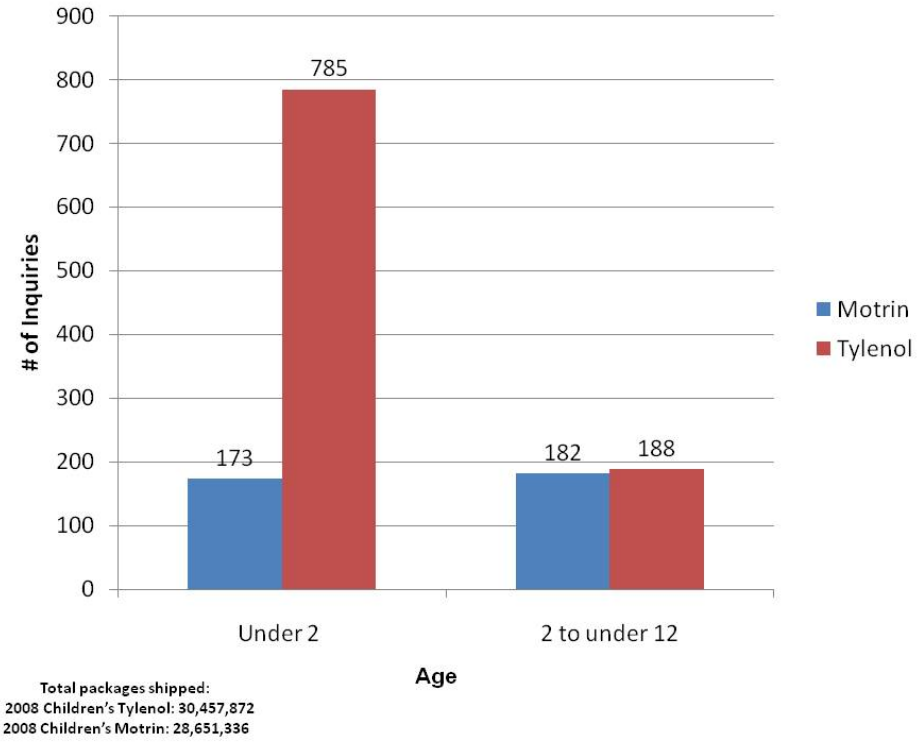
6.4.1 Published / Unpublished Clinical Data Demonstrate Efficacy and Safety of Acetaminophen in Children < 2 Years of Age

The safety and efficacy of acetaminophen has been evaluated through numerous pediatric studies that have included children < 2 years of age, or were conducted solely in children in this age group. McNeil has compiled a comprehensive listing of individual clinical trials, including 13 studies sponsored by McNeil (2 placebo controlled and 11 active controlled) and 84 published trials studying fever reduction, pain relief (associated with ear and throat, dental, and surgical pain) and pediatric immunizations [3]. Of the 84 acetaminophen published trials, 73 evaluated over-the-counter (OTC) or professional dose recommendations, and 11 studies evaluated higher dose levels and/or a prescription intravenous formulation. McNeil plans to provide a summary of these clinical trial data to its Citizens' Petition under review by FDA.

6.4.2 Calls to McNeil's Customer Care Center Demonstrate the Need for Dosing Information on Acetaminophen Labeling for Medications Intended for Use in Children < 2 Years of Age

In 2008, 33,700 of the calls received by McNeil's Consumer Care Center (CCC) were for inquiries pertaining to its OTC pediatric products. Of the 14,840 calls that pertained specifically to Children's Tylenol and Children's Motrin, 11,070 (75%) were for the former and 3,770 (25%) were for the latter. Dosing-related inquiries accounted for comparable portions of the calls for Children's Tylenol and Children's Motrin, specifically 1149 (10.4%) for the former and 494 (13.1%) for the latter. Figure 6-2 shows that the dosing-related inquiries for Children's Tylenol were heavily weighted (68%) toward children < 2 years of age, while those for Children's Motrin were distributed equally between the two age groups.

Figure 6-2 Dosing Inquiries by Age for Tylenol and Motrin in 2008



When one considers these data along with the fact that the consumer labeling for Infant's Motrin contains dosing instructions for children 6 months to < 2 years of age, while that of Children's Tylenol does not, it is reasonable to infer that the potential for consumer confusion regarding dosing —and hence the need to contact the manufacturer's call center—is reduced by having dosing instructions for children 6 months to < 2 years of age on the product label.

6.5 Pharmacokinetic-Pharmacodynamic Data Support Proposed Dosing Schedules

6.5.1 Proposed Pediatric Dosing Schedule for Children < 2 Years of Age is Adequate

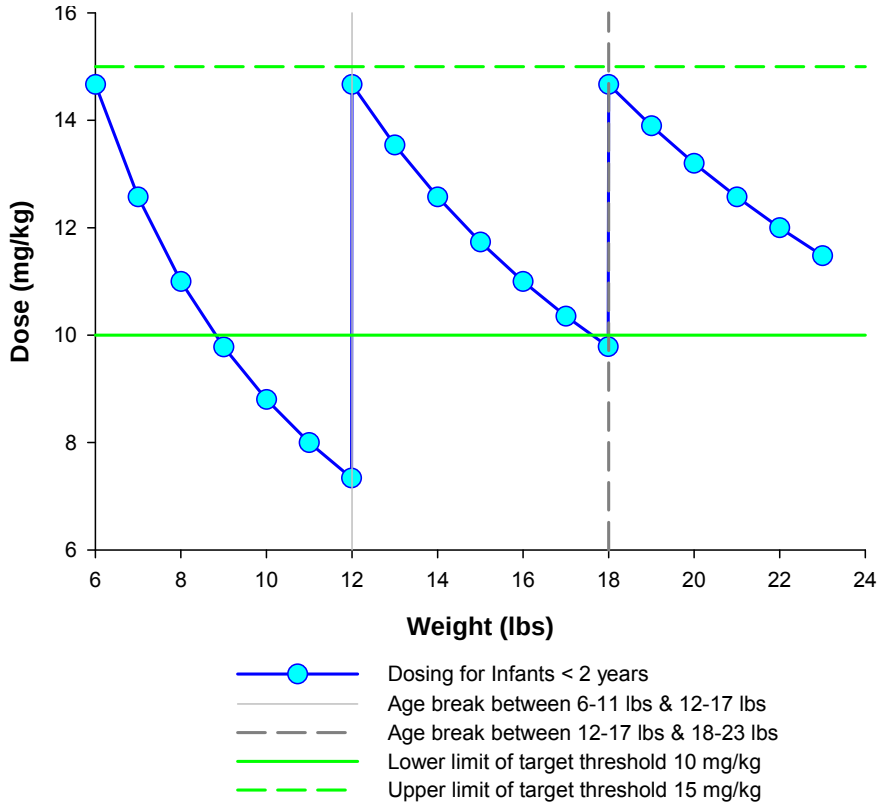
In 1983 McNeil, on its own initiative, developed an age-based and a weight-based dosing scheme to guide health-care professionals. This was based on dosing schedules first proposed in a publication in 1983 by Temple [4]. Currently, the weight- and age-based dosing scheme listed in Table 6-1 for children 6 months to < 2 years is provided as part of

the professional dosing information for acetaminophen. Based on this scheme, children < 2 years of age receive doses of 7.3 to 14.7 mg/kg (Figure 6-3).

Table 6-1 McNeil Professional Dosing Information for Children < 2 Years of Age

Weight (lbs)	Age (months)	Acetaminophen Dose (mg)	Dosing Regimen	Maximum Recommended Daily Dose (mg)
6-11	0-3	40	Every 4 hours, not to exceed 5 doses in 24 hours	200
12-17	4-11	80		400
18-23	12-23	120		600

Figure 6-3 Graphical Representation of the Current Weight--Based Professional Dosing Information for Children < 2 Years of Age



McNeil's currently recommended (Professional Dosing Information) dosing regimen, on a milligram per kilogram basis, results in doses between 10 and 15 mg/kg for most children < 2 years of age, except for the heavier infants in the 0 to 3 month age range, for whom

doses are less than 10 mg/kg but greater than 5 mg/kg (Figure 6-3). Since frequency of dosing is flexible and allows for up to a maximum of five doses, caregivers have the opportunity of dosing every four hours if adequate pain/fever relief is not achieved. The range of concentrations achieved within an individual is likely to be adequate for most children < 2 years.

Based on published pharmacometric analyses[1] of acetaminophen, it appears that the current dosing recommendation is reasonable for this young pediatric population, while providing simple guidelines to parents and caregivers for dosing. Some of the pharmacometric principles that have tested the concentration-response relationships of acetaminophen in children are described in sections below. McNeil believes that adequate pediatric pharmacokinetic and clinical data for acetaminophen are available to support pediatric dose selection in children < 2 years of age, and will provide these data to FDA as part of our pending Citizen Petition.

6.5.2 Acetaminophen Pediatric Dosing Based on Pharmacokinetics and Body Size

Anderson and Holford have published an extensive review on mechanism-based concepts of size and maturity in pharmacokinetics that are relevant to the determination of pediatric dosing [5]. Size models play a significant role in determining pediatric pharmacokinetic parameter estimates and, consequently, drug doses for children, but they have limitations [5,6].

Body weight has been used most commonly to scale for size in dosing rules, although it is recognized that there is a nonlinear relationship between weight and dose. Although the weight-based models tend to give the best estimates of infant doses based on precision and bias, these tend to underestimate doses across the entire pediatric population [7].

Allometric scaling of pharmacokinetic parameters is more mechanistic and takes into account physiological differences in different pediatric subgroups and adults. This approach can distinguish the effect of size from that of other covariates that show a high degree of co-linearity [8]. The allometric 3/4-power of weight model has been shown to be

[1] Pharmacometrics is an emerging science designed to inform decisions, such as dose selection, by conducting quantitative analysis of pharmacokinetic (and pharmacodynamic, efficacy, or safety) data.

useful for normalizing a large number of physiological parameters across species and age groups, and may be useful as a pediatric dosing rule based on drug clearance [6].

In the literature, a steady-state acetaminophen concentration of 10 µg/mL is purported to be efficacious both for antipyretic and analgesic activity [9,10]. Using allometrically weight-scaled pharmacokinetic parameters, and modeling and simulation of plasma concentrations, Anderson et al [11] have proposed a dosing regimen that includes a combination of loading and maintenance doses. This dosing paradigm can work in a hospital setting, but may be confusing to parents and caregivers. His dosing regimen would provide a target dose of 15 mg/kg in 50% of children < 2 years of age.

Also, van der Marel et al [12] have reported analgesic activity at less than 10 µg/mL in infants undergoing craniofacial surgery. It is possible that a range of concentrations is associated with graded analgesic and antipyretic effects. Therapeutic effects of antipyresis are likely to be affected by factors such as etiology of fever, intensity, circadian rhythm, and changing baseline. Similarly perception of analgesia is affected by placebo, circadian rhythm, social and psychological perceptions, and maturation of pain pathways [13].

6.5.3 Single-Dose and Steady-State Pharmacokinetics of Acetaminophen are Adequately Defined in Children < 2 Years of Age

The single- and multiple-dose pharmacokinetics in neonates, infants and young children have been described in several studies (Table 6-2), although studies that evaluate steady-state pharmacokinetics of acetaminophen in young children are few (Table 6-3). Given a half-life of about two hours, the drug would reach steady state in about 10 hours. Hence, data from 2 to 3 days of continuous dosing will reflect steady-state conditions.

Taken together, the data presented in Table 6-2 and Table 6-3 suggests that children are efficient in eliminating acetaminophen through alternative metabolic pathways versus adults. Although the Nahata study [19] suggests that acetaminophen accumulates in young children upon multiple dosing, these data are not borne out or confirmed by other literature. In fact, more recent literature in both adults [14,15] and neonates [20] suggests that acetaminophen induces UGT enzymes and induces its own metabolism via this non-toxic pathway.

Table 6-2 Summary of Pharmacokinetics Data as Mean (SD) for Children < 2 Years of Age

Citation & Population	Dose & Route	Age range	N	Cmax (µg/mL)	AUCinf (µg·h/mL)	Vd/F	CL/F	$T_{1/2}$ (h)	Metabolism Summary	Comments
Brown 1992 [16] Febrile children	12.5 mg/kg Oral (Tylenol elixir)	3 mo – 12 years	47	9.53	35.42 [a]	1.034 [a] L/kg	0.431 [a] L/h/kg	1.91[a]	NR	PK data for APAP were not separated out by age groups of <2yrs and >2 yrs
Lingen 1999 [17] Preterm neonates	20 mg/kg[b] Rectal	28-32 weeks (group 1)	21	12.5 (2.9)	95.1 (28.0)	NR	0.10 L/h (0.04)	11.0 (5.7)	Drug excreted mainly as APAP-S; 61% dose recovered in urine; G:S ratio 0.12	Dose range in group 1 was 16.6-26.6 mg/kg & group 2 was 17.1-22.1 mg/kg; all doses > 18 mg/kg in group 1 achieved therapeutic concentration (10-20 mg/L), but not in group 2
		32-36 weeks (group 2)	7	7.5 (4.0)	71.7 (41.7)	NR	0.56 (0.66)	4.8 (1.2)	Drug excreted mainly as APAP-S; 74.2% dose recovered in urine; G:S ratio 0.28	
Van der Marel 2001 [18] Children undergoing major craniofacial surgery	40 mg/kg LD + 20 mg/kg PO q6h (3 doses)	6-20 mo	20		144.3 [c]					
	40 mg/kg LD + 20 mg/kg rectally q6h (3 doses)	8-15 mo	20		171.2 [c]					

a: N=43;
b: 20 mg for birth weights 750-1249 g, 30 mg for 1250-1749 g, 40 mg for 1750-2250 g
c: $AUC_{5\text{-}20h}$

Abbreviations: APAP – acetaminophen; AUCinf – area under the curve to infinity; Cmax – maximum concentration; CL/F – oral drug clearance; G-glucuronide; LD – loading dose; PK – pharmacokinetics; PO – orally; NR – not reported; SD – standard deviation; S-sulfate; T½ - elimination half-life, Vd/F - volume of distribution

Table 6-3 Mean (SD) Single-Dose and Steady-State Pharmacokinetics of Acetaminophen

Citation / Population	Route of Administration / Duration of Dosing	N	Age range	Dose of APAP (mg/kg)	CL/F (L/h/kg)	CLss/F (L/h/kg)	Comment
Nahata [19] [a] Febrile infants	Oral/1 to 3 days	8	0.54-1.75 y	19 (6.9) Total Daily dose: 76.13 (5.77); dosing frequency: q 6 ±2.1 h	0.357 (0.087)	0.305 (0.088)	Given the small sample size, the validity of statistical differences is unclear
Neonates (postoperative pain)	IV [b] for 4 days (approx 15 doses each)	50	32-45 weeks (PMA)	PMA: 28 to <32 wks: 10 mg/kg; 32 to <36 wks 12.5 mg/kg; ≥ 36 wks 15 mg/kg; dosing frequency q6h (prn)		0.177 [c]	Clearance estimates using population PK approach; data were collected opportunistically after 2 -17 doses; CL increased with increasing PMA; CL reported for 46 weeks PMA; doses of 15 mg/kg q 6h resulted in mean serum concentrations of 10 mg/L
Allegaert [20] Neonates (postoperative pain)	IV [b] (inferred to be 3 to 4 days)	23[d]	29 to 60 wks postconceptional age (PCA); 1-137 postnatal age	15 mg/kg loading dose + maintenance dose by PCA: 10 mg/kg q8h for PCA ≤ 36 wks or 10 mg/kg q6h for PCA > 36 wks			Median APAP-G: 0.58 mmol/L Median APAP-S: 2.16 mmol/L Median free acetaminophen: 0.1 mmol/L G/T ratio:14% S/T ratio:72% G/S ratio: 0.27 Repeat collection: ↑ G/T ratio (8 to 16%), ↑ G/S ratio (13 to 21%), ↓ F/T ratio (14 to 9%), ↔ S/T ratio (74 to 72%); increase in glucuronidation with postnatal & PCA; decrease in free APAP with PCA; increase in glucuronidation with repeat administration suggesting induction observed in all 18 subjects

a: Data from Nahata et al was used for calculation of clearance parameters for infants < 2 y (data for 2 children >2 y is excluded)
b: Dosed as prodrug propacetamol; all parameters reported for acetaminophen including dose (=using ½ dose of propacetamol)
c: CLss not CL/F
d: 18 neonates with repeat urine metabolite measurements
Abbreviations: APAP – acetaminophen; CL/F – oral drug clearance; CLss/F – oral drug clearance at steady state; G - glucuronide; IV – intravenous; SD – standard deviation; S - sulfate; T - total; PMA – post menstrual age; PCA-post conceptional age; PK - pharmacokinetics

6.5.4 Developmental Differences in Metabolism Do Not Impair Metabolism of Acetaminophen Due to Multiple/Alternate Metabolic Pathways

Growth and development influence the pharmacokinetics of drugs. Since growth and development are rapid during neonatal period and during infancy, the pharmacokinetics of drugs may be different during this period than during adulthood. This may, in turn, affect the choice of drugs or doses of drugs.

Metabolism of most drugs, particularly acetaminophen, involves many enzymes and enzymatic pathways. While some enzymes may not be fully mature at birth, others may be expressed at high levels. Hence, for drugs such as acetaminophen, which are not dependent on a single enzyme for metabolic clearance, the overall picture for clearance mechanisms is complex. Some of the ambiguity and confusion stems from the conventional use of linear per kilogram scaling models. Anderson and Holford [21,22] have demonstrated that the allometric $3/4^{th}$ power model of weight is useful in normalizing and comparing pediatric data (including neonatal and infants) with adult estimates.

Acetaminophen undergoes extensive metabolism by oxidative Phase I and conjugative Phase II enzymes. Only about 2% to 5% of a dose is excreted unchanged in urine. About 5% to 10% of an acetaminophen dose is oxidized by cytochrome P4502E1 (CYP2E1) to produce NAPQI [23], a highly reactive, short-lived electrophile, which is subsequently conjugated with glutathione. The contribution of CYP isoenzymes, other than CYP2E1, to NAPQI formation is negligible in humans [24]. A small fraction of an acetaminophen dose is oxidized by cytochrome P4502A6 (CYP2A6) to form stable nontoxic catechols eventually found in the urine as sulfate and glucuronide conjugates [25]. Acetaminophen is mainly conjugated with glucuronic acid by UGT enzymes, specifically the isoforms UGT1A6 and UGT1A9 [26,27]. It is also a substrate for two sulfotransferases, SULT1A1 and SULT1A3 [28,29].

The clearance mechanisms of acetaminophen have been studied along the continuum of ages from fetal to infants through childhood and adults [30,31]. Clearance mechanisms mature and change through different phases of life. As shown in Table 6-4, it appears that during infancy, sulfation may be the most important clearance mechanism for acetaminophen, with glucuronidation being lower, as is evidenced by the altered G:S ratios.

Table 6-4 Metabolism and Elimination of Acetaminophen in Pediatric Population

Population	N	Age range	Dose	T½ (h)[a]	Metabolism Summary
Neonate [30]	12	2-3 day old, full term	12 mg/kg, SD, oral	3.5 (0.85)	Urinary excretion (% dose): unmetabolized APAP: 2.43 (0.86) APAP-G: 12.8 (4.1) APAP-S: 47.6 (8.1)
	Comment: Total recovery ~ 63%; limited capability of neonates for glucuronidation (~1/4th of adults) but well developed sulfation (higher than adults)				
Neonate	3	Newborn (1-3 days)	10 mg/kg, oral	4.9 (0.9)[b]	Urinary G:S ratio = 0.34
Children	7	3-9 y		4.5 (0.6)[b]	Urinary G:S ratio = 0.75
	4	12 y		4.4 (0.7)[b]	Urinary G:S ratio = 1.61
Adults [31]	4	Adult (23-30y)		3.6 (0.1)[b]	Urinary G:S ratio = 1.80
	Comment: Total recovery ~ 70% infants, ~80% others; overall rate of elimination of acetaminophen was similar across age groups; age-related differences were observed in glucuronidation and sulfation; adult pattern of elimination was observed by age 12 years				

a: mean (sd); b: calculated from urine data

Abbreviations: APAP – acetaminophen, APAP-G – acetaminophen glucuronide; APAP-S - acetaminophen sulfate; G:S - glucuronide/sulfation metabolite ratio, SD - standard deviation; T½ - elimination half-life

CYP2E1 is expressed in the fetal liver starting during the second trimester. The expression level increases through third trimester to post-birth [32]. During infancy, especially before 90 days after birth, the CYP2E1 enzyme expression is lower than adults, thereby reducing the formation of the reactive/toxic NAPQI intermediate. In these infants, a greater fraction of the administered acetaminophen dose is excreted unchanged in the urine versus adults.

6.6 Regulatory History for Labeling of Acetaminophen Products with Dosing Instruction for Children Under 2 Years of Age

For many years, FDA has held the position that dosing information for children < 2 years of age should not be included in the consumer labeling of acetaminophen-containing products, because the absence of this information would compel parents and caregivers to obtain this dosing information directly from a physician [33].

In January 1995, an FDA Nonprescription Drug Advisory Committee (NDAC) meeting was held to discuss dosing issues pertaining to pediatric OTC drug products [34]. At this

meeting, McNeil recommended that dosing instructions for children < 2 years of age be added to the labeling of pediatric analgesics and antipyretics, a position that was supported by many of the healthcare professionals that were in attendance [35]. The rationale behind this position was that many parents and caregivers were not contacting physicians for dosing information and that those who were contacting physicians often were receiving dosing information that was inaccurate.

In September 1997, a follow-up NDAC meeting was held at which panel members concluded that the age limit for the dosing of pediatric analgesics and antipyretics should be lowered to include children < 2 years of age [36]. FDA subsequently provided guidance stating that any manufacturer seeking such a labeling change would need to submit a request to the agency [37]. In response to this, McNeil submitted an sNDA in June 1998 for Concentrated Motrin Infants' Drops requesting dosing instructions for children < 2 years of age [38] and a citizen petition in February 1999 (CP-14, 77N-094) requesting an amendment to the internal analgesics tentative final monograph (TFM) that would allow dosing instructions for children < 2 years of age to be added to the consumer labeling of acetaminophen-containing products intended for use in this age group [39]. In April 1999, FDA approved the sNDA for Motrin Infants' Drops and the inclusion of a dosing range of 6-23 months on the product's consumer labeling [40].

Regarding the citizen petition, a teleconference took place in September 2000, at which time FDA requested additional information, including a review of the impact of newly published NHANES data on the age- and weight-based dosing schedules being proposed by McNeil [41]. In response to this request, McNeil submitted an amendment to its citizen petition in August 2001 that included this additional information [42]. Support for this petition was later expressed by the Director of the Division of OTC Drug Products at the NDAC meeting for OTC analgesics labeling in September 2002 [43].

Although having approved labeling for ibuprofen-containing for children < 2 years of age several years ago, FDA has not taken action to include dosing instructions for children < 2 years of age on the consumer labeling of acetaminophen-containing products [44]. McNeil believes that dosing instructions for children < 2 years of age should be added to the labeling for acetaminophen-containing products intended for use in this age group, and will continue to work with FDA on our request.

6.7 Conclusions

Acetaminophen has been shown to be a safe and effective antipyretic and analgesic. To decrease a preventable root cause of acetaminophen dosing errors and decrease consumer confusion, dosing instructions for children < 2 years of age should be included on the label of acetaminophen-containing pediatric products. The concentrated acetaminophen drops, which when accompanied by dosing information, can be used safely by parents and caregivers as demonstrated by the safe use of similar ibuprofen-containing concentrated drops.

6.8 Reference List

1. American Academy of Pediatrics. http://www.aap.org/publiced/BK0_Colds.htm Accessed on June 2, 2009
2. American Academy of Pediatrics and the American Academy of Family Physicans. Diagnosis and Management of Acute Otitis Media. March 2004. http://www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/clin_recs/otitismedia.Par.0001.File.dat/final_aom.pdf Accessed on June 2, 2009.
3. Listings of clinical trials on file at McNeil.
4. Temple AR. Pediatric dosing of acetaminophen. Pediatr Pharmacol 1983; 3: 321-327.
5. Anderson BJ, Holford NHG. Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–332.
6. Anderson BJ, Meakin GH. Scaling for size: some implications for paediatric anaesthesia dosing. Paediatr Anaesth 2002;12:205-219.
7. Johnson TN. The problems in scaling adult drug doses to children. Arch Dis Child 2008;93:207-211.
8. Meibohm B, Laer S, Panetta JC, et al. Population pharmacokinetic studies in pediatrics: Issues in design and analysis. *AAPS J* 2005;7:E475-E487 Article 48 (http://www.aapsj.org).
9. Anderson BJ, Holford NH, Woollard GA, Chan PL. Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. Br J Clin Pharmacol 1998; 46: 237-243.
10. Anderson BJ, Holford NH, Woollard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. Anesthesiology 1999; 90: 411-421.
11. Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. Br J Clin Pharmacol 2000; 50: 125-134.
12. van der Marel CD, van Lingen RA, Pluim MA, Scoones G, van Dijk M, Vaandrager JM, Tibboel D. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clin Pharmacol Ther. 2001;70:82-90.
13. Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child. 2008;93:241-7.
14. Hendrix-Treacy S, Wallace SM, Hindmarsh KW, Wyan GM, Danilkewich A. The effect of acetaminophen administration on its disposition and body mass of sulphate. Eur J Clin Pharmacol 1986; 30273-8.
15. Gelotte CK, Auiler JF, Lynch JM, et al. Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. Clin Pharmacol Ther 2007;81:840-848.
16. Brown RD et al: J Clin Pharmacol 1992; 32:231-241
17. van Lingen RA, Deinum JT, Quak JM, Kuizenga AJ, van Dam JG, Anand KJ, Tibboel D, Okken A. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. Arch Dis Child Fetal Neonatal Ed 1999; 80: F59-63.

18. van der Marel CD, van Lingen RA, Pluim MA, Scoones G, van Dijk M, Vaandrager JM, Tibboel D. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clin Pharmacol Ther. 2001;70:82-90.

19. Nahata MC, Powell DA, Durrell DE, Miller MA. Acetaminophen accumulation in pediatric patients after repeated therapeutic doses. Eur J Clin Pharmacol 1984; 27: 57-59.

20. Allegaert K, de Hoon J, Verbesselt R, Vanhole C, Devlieger H, Tibboel D. Intra- and interindividual variability of glucuronidation of paracetamol during repeated administration of propacetamol in neonates. Acta Paediatrica 2005; 94; 1273-79.

21. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48: 303-332.

22. Anderson BJ, Holford NH. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24:25-36.

23. Dahlin DC, Miwa GT, Lu AYH, et al. N-acetyl-p-benzoquinone imine: A cytochrome P450-mediated oxidation product of acetaminophen. Proc Natl Acad Sci USA 1984;81:1327–1331.

24. Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000;67:275–282.

25. Chen W, Luke L, Stella J, et al. Oxidation of acetaminophen to its toxic quinone imine and nontoxic catechol metabolites by baculovirus-expressed and purified human cytochromes P450 2E1 and 2A6. Chem. Res. Toxicol 1998;11:295–301.

26. Court MH, Duan SX, Von Moltke LL, et al. Interindividual variability in acetaminophen glucuronidation by human liver microsomes: Identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. J Pharmacol Exp Ther 2001;299:998-1006.

27. Burchell B. Genetic variation of human udp-glucuronosyltransferase implications in disease and drug glucuronidation. Am J Pharmacogenomics 2003;3:37-52.

28. Reiter C. Weinshilboum R. Platelet phenol sulfotransferase activity: Correlation with sulfate conjugation of acetaminophen. Clin Pharmacol Ther 1982;32:612-621.

29. Pacifici GM. Inhibition of human liver and duodenum sulfotransferases by drugs and dietary chemicals: A review of the literature. Int J Clin Pharmacol Ther 2004;42:488-495.

30. Levy G, Khanna NN, Soda DM, Tsuzuki O, Stern L. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and d-glucaric acid excretion. Pediatrics 1975; 55: 818-825.

31. Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children, and adults. Clin Pharmacol Ther 1976;19:284-94.

32. Johnsrud EK, Koukouritaki SB, Divakaran K, Brunengraber LL, Hines RN, McCarver DG. Human hepatic CYP2E1 expression during development. J Pharmacol Exp Therap 2003; 307: 402-07.

33. U.S. Food and Drug Administration. Notice of Proposed Rulemaking. Internal Analgesic, Antipyretic, and Antirheumatic Drug products for Over-the-Counter Human Use; Tentative Final Monograph. Federal Register Vol. 53 No. 221, Wednesday, November 16, 1988.

34. U.S. Food and Drug Administration. Summary Minutes of Nonprescription Drugs Advisory Committee Meeting – January 13, 1995.

35. U.S. Food and Drug Administration. Summary Minutes of Nonprescription Drugs Advisory Committee Meeting – January 13, 1995.

36. U.S. Food and Drug Administration. Transcript of Nonprescription Drugs Advisory Committee Meeting – September 18, 1997.

37. U.S. Food and Drug Administration. Letter to McNeil Consumer Products Company. June 8, 1998.

38. McNeil Consumer Products Company. Supplemental New Drug Application to U.S. Food and Drug Administration. June 15, 1998.

39. McNeil Consumer Healthcare. Citizen Petition to Amend the Tentative Final Monograph for Internal Analgesic, Antipyretic and Antirheumatic Drug products for Over-the-Counter Use – Expanded Age Groups for OTC Consumer Dosing Instructions covering Acetaminophen. February 1, 1999.

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

41. McNeil Consumer Healthcare. Amendment to Citizen Petition dated 2/1/99 Expanded Age Groups for OTC Consumer Dosing Instructions Covering Acetaminophen. August 15, 2001.

42. McNeil Consumer Healthcare. Amendment to Citizen Petition dated 2/1/99 Expanded Age Groups for OTC Consumer Dosing Instructions Covering Acetaminophen. August 15, 2001.

43. U.S. Food and Drug Administration. Transcript of Nonprescription Drugs Advisory Committee Meeting – September 19-20, 2002. Available at http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T1.htm,, http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3882T2.htm.

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

SECTION 7 CONSUMER NEED FOR OTC COMBINATION MEDICINES

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7 CONSUMER NEED FOR OTC COMBINATION MEDICINES

7.1 FDA's Areas of Concern

FDA has proposed eliminating OTC combination acetaminophen medicines as Option 5a in the document titled, Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury, included in FDA's May 22, 2009 background package for the June 29-30, 2009 joint advisory committee meeting. FDA states that the intended effect of eliminating OTC combination acetaminophen medicines is "This could help prevent overdose resulting from unknowingly taking multiple OTC acetaminophen containing medicines. This option would possibly also reduce the incidence of consumers combining OTC acetaminophen-containing products with Rx products containing acetaminophen, especially when the Rx acetaminophen product is not clearly labeled, or is labeled as APAP."

7.2 Key Points

- Adults use the combination of acetaminophen and diphenhydramine to treat pain with sleeplessness as it is effective in the treatment of both symptoms and is well tolerated.

- For the symptomatic relief of the common cold in children and adults, it is important to continue to provide for OTC use of acetaminophen combination-ingredient cough and cold medicines as an appropriate treatment option.

    - Children and adults commonly develop acute respiratory tract infections (colds) with one or more symptoms including nasal congestion, cough, runny nose, pain, and fever.

    - The use of combination medicines reduces the likelihood of dosing errors since patients and consumers administer one medicine, instead of several medicines, for relief of all of their symptoms. The use of combination medicines eliminates the need for the consumer to review and understand the dosing and Drug Facts on multiple medicines, some of which may have different dosing intervals. This simplifies medication administration, thus reducing the opportunity for dosing errors.

    - Single ingredient and combination-ingredient cough and cold medicines have similar safety profiles with a very rare occurrence of serious adverse events.

- Caregivers appropriately use both single-ingredient and combination-ingredient OTC cough and cold medications.

7.3 Treatment of Symptom Complexes

Having both single- and combination-ingredient medicines available is beneficial to adults and children because it allows for treatment of the specific symptoms of an illness such as a cold or pain with sleeplessness. As discussed in greater detail in Section 7.7.1, cold symptoms in children and adults vary in number and type, and in which symptoms occur in combination. The availability of medicine choices with various combinations of cough and cold ingredients allows patients and consumers to tailor treatment to the specific cold symptoms with one medicine instead of taking individual medications to treat each symptom.

7.4 Simplified Medication Administration

The use of combination medicines reduces the likelihood of dosing errors since patients and consumers administer one medicine, instead of several medicines, for relief of all of their symptoms. The use of combination medicines eliminates the need for the consumer to review and understand the dosing and Drug Facts on multiple medicines, some of which may have different dosing intervals. This simplifies medication administration, thus reducing the opportunity for dosing errors.

In addition, combination medicines make it easier to administer treatments to children; parents and caregivers can use one medicine to treat multiple symptoms instead of using multiple medicines to treat multiple symptoms. Children are more likely to be compliant with taking one combination medicine than with taking multiple single-ingredient medicines, which likely translates into better relief of the cold symptom complex. Data from studies of fixed-dose combination-ingredient prescription medicines are supportive and demonstrate improved adherence, reduced pill burden and costs, and improved outcomes with the use of fixed-dose combination-ingredient medicines compared to use of multiple mono-ingredient medicines [1,2,3,4].

7.5 Reduced Cost to Patients and Consumers

Combination medicines reduce the overall cost of treating a cold/flu. Ninety-three percent (93%) of cold sufferers report having multiple symptoms during a cold. Without combination medicines, they would need to purchase multiple medicines to treat their

multiple symptoms. The purchase of a separate pain reliever in addition to their cough/cold medicine increases the total cost to the consumer for symptom treatment by 31%.

7.6 Treatment of Pain with Sleeplessness with an OTC Combination Medicine in Adults

Adults experience pain with sleeplessness and the OTC combination medicine of acetaminophen and diphenhydramine is commonly used by consumers to treat this conditon.

Three studies have shown that the combination of acetaminophen 1000 mg and diphenhydramine 50 mg is more effective in the treatment of pain with sleeplessness than either of the individual components alone or placebo. One randomized, double-blind, placebo-controlled, single-dose study conducted by McNeil [5] evaluated the efficacy and safety of acetaminophen 1000 mg with diphenhydramine 50 mg at bedtime in 372 subjects with osteoarthritis pain and sleeplessness compared with acetaminophen 1000 mg, diphenhydramine 50 mg, or placebo. The combination was significantly superior to acetaminophen alone for four subject-assessed sleep outcomes (time to final awakening/sleep duration, global assessment, quality of sleep, and how rested the next day) and significantly superior to diphenhydramine alone for four subject-assessed pain outcomes (pain at time of first awakening, pain relief at time of both first and final awakening, and global pain assessment).

The second randomized, double-blind, placebo-controlled, single-dose study conducted by McNeil [6] evaluated the efficacy and safety of acetaminophen 1000 mg with diphenhydramine 50 mg at bedtime in 80 subjects with osteoarthritis pain and sleeplessness compared with acetaminophen 1000 mg, diphenhydramine 50 mg, or placebo. Using EEG sleep latency measures, the combination was significantly superior to acetaminophen alone for total sleep time, total recording time, and the percent of time spent asleep. The combination was also significantly superior to acetaminophen alone for the subject-assessed sleep outcomes of time to final awakening and global sleep assessment and significantly superior to diphenhydramine alone for the subject-assessed pain outcome of pain relief at time of first awakening.

Pain with sleeplessness was also evaluated in a proof-of-concept dental pain study [7]. This study evaluated the feasibility of the dental pain model to assess the effects of acetaminophen 1000 mg/diphenhydramine 50 mg, acetaminophen 1000 mg, and placebo on sleep in subjects post-oral surgery with phase-shifted sleep. Eighty-six subjects aged 16 to 29 years of age were enrolled in this randomized, double-blind, single-dose study. Subjects had surgical removal of up to two third molars including one (but not two) mandibular third molars at least partially impacted in either tissue or bone. Subjects stayed overnight at a research center and were required to go to bed at least five hours earlier than

usual. This study demonstrated the significant individual contributions of both acetaminophen and diphenhydramine to the analgesic/sleep aid combination. The primary endpoint of total sleep time, as assessed by actigraphy, was statistically significantly longer for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine 50 mg compared with those treated with acetaminophen 1000 mg and compared with those treated with placebo. The global assessment of study medication as a pain reliever was statistically significantly greater for subjects treated with the combination of acetaminophen 1000 mg/diphenhydramine 50 mg or with acetaminophen 1000 mg compared with those treated with placebo. All study medications were well tolerated.

All three of these studies demonstrated that the combination of acetaminophen 1000 mg and diphenhydramine 50 mg was effective for pain relief and sleep maintenance and quality and was well tolerated.

7.7 OTC Combination Cough and Cold Medicines are an Important Treatment Option for the Symptomatic Relief of the Common Cold in Adults and Children

The use of OTC combination-ingredient cough and cold medicines is an appropriate treatment option for the symptom complexes observed with the common cold. Both adults and children experience multiple symptoms with the common cold, with many being similar between the two groups.

7.7.1 Multiple Symptoms of the Common Cold

Children and adults commonly develop acute respiratory tract infections (colds) with one or more symptoms including nasal congestion, cough, runny nose (rhinorrhea), pain, and fever. The majority of these symptoms are experienced concurrently. Use of multiple-ingredient medicines to treat these symptoms in children has been reported to range from 64% to 70% [13,14,20]. The percentage of older children and adults (10 years and older) with four or more symptoms treatable with medicines containing ingredients in each of the following four categories (antitussive, antihistamine, decongestant, analgesic) has been reported to range from 45% to 57% [16,17]. In addition, the percentage of children and adults with symptoms treatable with medicines containing ingredients in three of the four categories has been reported to range from 16% to 56% [13,16,17].

Table 7-1 provides a summary from both published and unpublished sources of the symptoms experienced by individuals with colds and the medications used for relief. The data presented focus primarily on children but where available in the study, adult data are also summarized.

Table 7-1. Summary of the Symptoms Experienced and Medications Used by Adults and Children With Colds From Published and Unpublished Sources

Reference	Number of Subjects (Age)	Findings
Pappas 2008 [8]	81 (5-12 y)	At their peak: nasal congestion (88%), runny nose (72%), cough (69%), sneezing (55%), headache (20%), feverishness (15%).
Gwaltney 1967 [9]	139 (adults – age not stated)	Rhinorrhea (50%) and sneezing (67%) occurred during days 1-3; sore throat (~50%) occurred during days 1-2; hoarseness (25%), cough (33%); headache (25%), occurred during days 1-3.
Hay 2005 [10]	13,617 (0-57 mo)	Children experiencing cough: <6 mo (65%), 6 to 17 mo (84%), 18 to 29 mo (86%), 30 to 41 mo (88%), 42 to 56 mo (92%). Majority of children less than 5 years of age experience cold (88% to 96%) or cough (65% to 92%) symptoms.
Kurugol 2007 [11]	120 (1-10 y)	Nasal drainage (94.2%), cough (89.2%), sore throat (69.2%), nasal congestion (61.7%), scratchy throat (55.8%), fever (52.5%), sneezing (48.3%), hoarseness (39.2%), headache (19.2%), muscle ache (18.3%).
Butler 2002 [12]	290 (1-12 y)	Coryza (80%), cough (79%), increased temperature (54%), pharyngitis (49%), enlarged lymph nodes (46%), malaise (45%).
Vernacchio 2008 [13]	439 (0-17 y)	Of the 489 medicines used, 35.8% were single-ingredient and 64.2% were multiple-ingredient. Multiple-ingredient medicines most commonly used were decongestant/first-generation antihistamine combinations (15.5%) and antitussive/decongestant/first-generation antihistamine combinations (10.4%). 16% of the cough and cold combination medicines used contained ingredients in 3 of the following 4 categories (antitussive, antihistamine, decongestant, analgesic). The reason given for use of the 489 medicines was cough (23.7%), cold (21.7%), allergy (19.6%), and not related to cough, cold, or allergy or unclear (35.0%).
Slone Epidemiology Center 2007 [14]	2857 (0-11 y) 1644 (12-17 y) 20518 (≥18 y)	Of children <12 y, 93.7% used a cough/cold medication, of which 64.1% was a multiple-ingredient medicine. For children <2 y, antihistamine, antitussive, and expectorant use were most common in those 12-23 mo, and decongestant use was highest in those 6-11 mo. Use of any of the cough/cold medications in infants <6 mo (6.2%), 6-11 mo (16%), 12-23 mo (12%). Use of any of the cough/cold medications: <2 y (12%), 2-5 y (12%), 6-11 y (8.5%), 12-17 y (6.5%), ≥18 y (10%).
Vicks Research Center 1983 [15]	3166 (2-12 y)	<u>Assessments by mothers</u> Symptoms commonly reported: any cough (60.2%), fever (56.4%), runny nose (42.2%), sore throat (34.4%), earache (32.8%). Most frequent combinations: cough with fever (33.6%), cough with runny nose (30.5%). <u>Assessments by physicians</u> Clinical findings commonly reported: any cough (48.5%), nasal congestion (47.7%), pharyngitis (46.7%), fever (44.2%), rhinorrhea (43.3%). Most frequent combinations: cough with nasal congestion (28.9%), cough with rhinorrhea (27.3%).

Table 7-1. Summary of the Symptoms Experienced and Medications Used by Adults and Children With Colds From Published and Unpublished Sources

Reference	Number of Subjects (Age)	Findings
Bristol Myers Products 1979 [16]	1000 (≥11 y)	Percent reporting: symptoms that required 4 of the 4 drug categories (57%), symptoms that required 3 of the 4 drug categories (30%). Percent reporting a symptom that required: an analgesic (88%), a decongestant (78%), an antihistamine (92%), an antitussive (82%).
Vicks Chemical Company 1978 [17]	322 (≥10 y)	45% experienced all 4 symptoms (nasal/head congestion, rhinorrhea, pain/fever/sore throat, and cough/phlegm) simultaneously on at least 1 day of their cold. 17% experienced all 4 symptoms simultaneously on 3 or more days of their cold. 56% experienced 3 of 4 symptoms on at least 1 day of their cold. Percent reporting: nasal/head congestion (85.1%), rhinorrhea (84.2%), pain/fever/sore throat (83.2%), cough/phlegm (64.3%).
Pagano 1983 [18]	1260 (0-17 y) 1942 (≥18 y)	For the children ≤17 y, 33% reported multiple symptoms of which 15% were cough/chest/nasal/throat, 15% were cough/chest/nasal, and 3% were cough/chest/sore throat. For the adults ≥18 y, 42% reported multiple symptoms of which 25% were cough/chest/nasal/throat, 13% were cough/chest/nasal, and 4% were cough/chest/sore throat.
2007 Ailment Diary 2008 [19]	671 (0-17 y)	Symptoms commonly reported: cough (76%), runny nose (63%), stuffy nose (37%). Most children reported 2 or more symptoms with 35% reporting 1 symptom only. Most frequently reported symptoms when: 1 symptom reported (coughing, 20%), 2 symptoms reported (coughing, 31%; runny nose, 24%; stuffy nose, 11%), 3 symptoms reported (coughing, 26%; runny nose, 26%; stuffy nose, 13%; chest congestion, 10%), 4 symptoms reported (coughing, 15%; runny nose, 16%; stuffy nose, 11%; sneezing, 11%), 5 or more symptoms reported (coughing, 12%; runny nose, 13%; stuffy nose, 11%; sneezing, 11%).
Gallup Survey 2008 [20]	759 (6 mo-11 y)	555 caregivers used OTC cough/cold medications for their children (70% multi-symptom). 391 caregivers used a multi-symptom cold medication to treat multiple symptoms at once for their child that contained a cough suppressant (72%), a decongestant (69%), a fever reducer/pain reliever (55%), an antihistamine (42%), and an expectorant (36%).
Forbes Consulting Group 2009 [21]	1491 (≥ 18 y)	93% of 1491 cold sufferers (consumers who had a cold in the past 6 months who used an OTC medication or who were likely to use an OTC medication to treat their cold) reported having multiple symptoms during their most recent cold. During their most recent cold, consumers reported an average of 8.1 symptoms. 58% of consumers reported that it was important that their cold medicine relieves all of their symptoms, not just one. Runny nose, stuffy nose, nasal/head congestion, sore throat and sneezing were the most commonly reported symptoms of a cold.

Table 7-1. Summary of the Symptoms Experienced and Medications Used by Adults and Children With Colds From Published and Unpublished Sources

Reference	Number of Subjects (Age)	Findings
Wisconsin Upper Respiratory Symptom Survey [22]	149 (18 – 80 y)	Participants with colds reported nasal symptoms (99%), cough (94%), sore or scratchy throat (91%), headache (88%), body ache (84%), sinus pain or pressure (80%), chest congestion (73%), feverishness (69%), chills (57%), and sweats (55%).

Abbreviations: mo = months, y = years

In a recent survey conducted by the Forbes Consulting Group, participants (18 years and older) were asked to identify which symptoms they tried to treat, manage or prevent [21]. Table 7-2. presents a summary of cold symptoms treated and those treated with an OTC medicine. Of the symptoms treated, analgesics provide relief of sore throat, headaches, sinus headache, sinus pain, fever, and body/muscle aches/pains; these symptoms are listed at the beginning of the table. Participants reported treating these six symptoms 67% to 84% of the time. Additionally, these six symptoms were treated with an OTC medicine 30% to 57% of the time.

Table 7-2. Summary of Symptoms Treated by Adult Cold and Flu Sufferers (n=2068) – Forbes Consulting Group 2009 [21]

Symptom	Treated %	Treated with OTC Medicine %
Sore Throat	84	57
Headaches	81	45
Sinus Headache	78	38
Sinus Pain	77	30
Fever	76	37
Body/Muscle Aches/Pains	67	41
Nasal/Head Congestion	88	60
Dry Hacking Cough	84	30
Sinus Congestion	82	48
Migraine Headaches	81	10
Cough with Phlegm	77	37
Sinus Infection	77	10
Stuffy Nose	76	55
Runny Nose	76	55
Sinus Pressure	74	41
Chest Congestion	71	41

The Wisconsin Upper Respiratory Symptom Survey provided data on new onset cold symptoms in 149 adults aged 18 to 80 years with colds [22]. Participants reported on their cold symptoms during 1,681 person-days of illness. As shown in Table 7-3, of the symptoms reported, analgesics provide relief of sore or scratchy throat, headache, sinus headache, sinus pain or pressure, feverishness, sweats, chills, and body ache; these

symptoms are listed at the beginning of the table. Participants reported these seven symptoms with a frequency of 57% to 91%.

Table 7-3. Summary of Symptoms in 149 Adults with Colds – Wisconsin Upper Respiratory Survey [22]

Symptom	Percentage with Symptom
Sore or scratchy throat	91
Headache	88
Sinus pain or pressure	80
Feverishness	69
Sweats	55
Chills	57
Body ache	84
Nasal symptoms	99
Cough	94
Chest congestion	73

Pappas and colleagues evaluated symptom diaries kept for 81 healthy, school-age children (5 to 12 years old) for 10 days after onset of a cold [8]. Table 7-4 presents a summary of the cold symptoms experienced by these children. The three symptoms most frequently reported at onset, at their peak, and that persisted the longest were nasal congestion, runny nose, and cough. At their peak, nasal congestion, runny nose, and cough were reported by 88%, 72%, and 69% of children, respectively. Seventy-three percent of children remained symptomatic 10 days after onset of illness.

Table 7-4. Summary of Symptoms Experienced by Children Age 5-12 Years for 10 Days After Onset of a Cold – Pappas et al 2008 [8]

	Percent of Children Reporting		
Symptom[a]	Onset	Peak (Day)	Persisting Through (Day)
Nasal Congestion	59%	88% (Day 3)	≥75% (Day 7)
Runny Nose	~58%	72% (Day 3)	≥50% (Day 6)
Cough	46%	69% (Day 1)	≥50% (Day 8)
Sneezing	36%	55% (Day 1)	≥35% (Day 5)
Headache	15%	20% (Day 1)	15% (Day 4)
Feverishness	15%	15% (Day 1)	Declined over first 3 days

a: Sore throat and hoarseness were not evaluated.

Pappas and colleagues [8] compared the data for the subset of 37 children in their study with colds due to rhinovirus with data from a study by Gwaltney and colleagues of 139 rhinovirus colds in adults [9]. The progression of cold symptoms was comparable between

adults and children, although minor differences were noted. Over 50% of children reported nasal congestion, runny nose, and cough during the first 5 days of illness, while the only symptom reported in over 50% of illnesses in adults was nasal discharge and that persisted only through Day 4. The duration of symptoms was longer in children than in adults; 73% of children were still reporting symptoms at Day 10 compared to 20% of adults. Cough in children peaked on Day 2 at over 70% and was reported in over 40% through Day 9, compared to cough in adults, which peaked at about 40% on Days 3 through 5 and then dropped to about 10% by Day 10.

In summary, children and adults frequently develop colds with one or more symptoms including nasal congestion, cough, runny nose (rhinorrhea), pain (headache, sore throat, sinus pain, body aches), and fever. The majority of these symptoms are experienced concurrently. Use of multiple-ingredient medicines to treat these symptoms in children and adults has been reported to range from 64% to 70% [13,14,20]. The percentage of older children and adults (10 years and older) with four or more symptoms treatable with medicines containing ingredients in each of the four categories (antitussive, antihistamine, decongestant, analgesic) has been reported to range from 45% to 57% [16,17]. In addition, the percentage of children and adults with symptoms treatable with medicines containing ingredients in three of the four categories has been reported to range from 16% to 56% [13,16,17].

7.7.2 Similar Safety Profile for Single-Ingredient and Combination Medicines

Single-ingredient and combination-ingredient pediatric and adult acetaminophen medicines have similar safety profiles, with a very rare occurrence of fatal or other serious adverse events. Table 7-5 provides a summary of reporting rates for fatal or other serious adverse events from the McNeil post-marketing adverse event data for acetaminophen single-ingredient and combination-ingredient medicines for a four-year period from January 2005 through December 2008. Exposure was based on sales of McNeil Consumer Healthcare medicines for the same period as available through IMS Health National Sales Perspective (NSP) data. These data indicate that fatal and other serious adverse event reporting rates are very low and similar for single-ingredient and combination-ingredient pediatric and adult acetaminophen medicines.

Table 7-5. Reporting Rates for Cases Coded as Fatal or Other Serious (Excluding Accidental Ingestion) per Million Doses Distributed, McNeil Consumer Healthcare Post-marketing Database, January 2005 – December 2008

	Age Group	
	< 12 years	≥ 12 years
OTC acetaminophen medicines		
Single ingredient	0.76	0.08
Combination ingredient	0.31	0.13

7.7.3 Caregivers Report Appropriate Use of Medicines

Parents appropriately use both single- and combination-ingredient OTC cough and cold medicines. An unpublished report on the use of cough and cold medication based on data from the Slone Survey, a national random-digit-dial telephone survey of medication use, obtained information from subjects interviewed between February 1998 and April 2007 and included data for 2857 children ages 0 to 11 years [14]. Parents were asked to report all prescription and OTC medications, vitamins and minerals, and herbals/supplements taken by their children during the preceding seven days, gathering the relevant containers whenever possible. Cough and cold medications included oral medications that contained one or more antitussive, decongestant, expectorant, or first-generation antihistamine (eg, chlorpheniramine and diphenhydramine). During this period, it was reported that in a given week 12.0% of children less than 2 years of age, 12.0% of children 2 to 5 years of age, and 8.5% of children ages 6 through 11 years used a cough and cold medication. Overall, it was reported that one cough and cold medication was used by 93.7% of children, of which 64.1% was a multiple-ingredient medicine. Two to three days of use of cough and cold medication per week was the most frequent category of duration of use reported, with percentages of children in this category ranging from 47.1% to 60.0% for various categories of cough and cold medications (antihistamine, decongestant, antitussive, and expectorant). Use for seven days per week was relatively infrequent, and ranged from 4.5% to 10.2%.

7.8 Summary

Children and adults commonly have multiple symptoms that benefit from treatment with combination-ingredient medicines. In children and adults, acute respiratory tract infections (colds) often have one or more symptoms including nasal congestion, cough, runny nose, pain, and fever. In adults, pain and sleeplessness are common symptoms that often are present simultaneously. Patients, consumers, caregivers and healthcare providers currently use both single ingredient and combination ingredient medicines when treating colds or pain and sleeplessness when one or more symptoms are present. In addition,

these medicines also reduce the likelihood of dosing errors because of a simplified dosing administration and they reduce the overall cost to the consumer of purchasing multiple medicines to treat multiple symptoms. Compliance is enhanced with combination medicines compared with use of multiple single-ingredient medicines administered to children and the elderly. Data demonstrate a similar safety profile for single-ingredient and combination acetaminophen medicines.

7.9 Reference List

1. Bangalore S, Parkar, S, Messerli, F. Compliance and fixed dose combination therapy. Am J Med 2007;120:713-719.

2. Rascati K, Akazawa, M, Johnsrud M, et al. Comparison of hospitalizations, emergency department visits, and costs in a historical cohort of Texas Medicaid patients with chronic obstructive pulmonary disease, by initial medication regimen. Clin Ther 2007;29:1203-1213.

3. Blonde L, Wogen, L, Kreilick, C., and Seymore, A. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin. Diabetes, Obesity and Metab 2003;5:424-431.

4. Melikian C, White J, Vanderplas A, et al. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002;24:460-467.

5. McNeil Consumer Products Company Clinical Study Report for Protocol 90-059: Effects of an acetaminophen-diphenhydramine combination on sleep in patients with pain secondary to osteoarthritis. Fort Washington, PA: McNeil Consumer Healthcare, August 1999 (data on file).

6 . McNeil Consumer Products Company Clinical Study Report for Protocol 91-159: Effects of acetaminophen-diphenhydramine combination on sleep in subjects with pain secondary to osteoarthritis as determined by out-patient EEG monitoring. Fort Washington, PA: McNeil Consumer Healthcare, February 1999 (data on file).

7. McNeil Consumer Healthcare Clinical Study Report for Protocol AADPWS4001: A proof-of-concept evaluation of the dental pain model to assess efficacy of acetaminophen 1000 mg/diphenhydramine HCl 50 mg. Fort Washington, PA: McNeil Consumer Healthcare, April 2009 (data on file).

8. Pappas DE, Hendley JO, Hayden FG, et al. Symptom profile of common colds in school-aged children. Pediatr Infect Dis *J* 2008;27:8-11.

9. Gwaltney JM, Hendley JO, Simon G, et al. Rhinovirus infections in an industrial population. JAMA 1967;202:494-500.

10. Hay AD, Heron J, Ness A, et al. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): A prospective cohort study. Fam Pract 2005;22:367-374.

11. Kurugol Z, Bayram N, Atik T. Effect of zinc sulfate on common cold in children: Randomized, double-blind study. Pediatr Int 2007;49:842-847.

12. Butler CC, Robling M, Prout H, et al. Management of suspected acute viral upper respiratory tract infection in children with intranasal sodium cromoglicate: A randomized controlled trial. Lancet 2002:359:2153-2158.

13. Vernacchio L, Kelly JP, Kaufman DW, et al. Cough and cold medication use by US children, 1999-2006: Results from the Slone Survey. Pediatrics 2008;122:e323-e329.

14. Slone Epidemiology Center at Boston University. Use of over-the-counter medications for cough/cold by children in the United States, 1998-2007. Final report of an analysis of data from the Slone Survey. October 12, 2007. (Data on file).

15. Vicks Research Center Medical Department Report for Protocol CRD#81-32: Pediatric URI Survey (Project 329). Shelton, Connecticut: Vicks Research Center, December 1983 (submitted to Federal Register Docket No. 76N-052G).

16. Bristol Myers Products. Incidence of symptoms and combinations of symptoms in the common cold. New York, New York. July 1979 (submitted to Federal Register Docket No. 76N-052G).

17. Vicks Chemical Company. A symptomatology profile of cold sufferers. 1978 (submitted to Federal Register Docket No. 76N-052G).

18. Pagano JP. Symptom Progression and Concurrency. December 1983 (submitted to Federal Register Docket No. 76N-052G).

19. TNS – The Sixth Sense of Business™. Ailment Diary: Pediatric UR – Cold Domain. TNS – The Sixth Sense of Business™, London, UK, September 2008. (Data on file).

20. Multi-sponsor Surveys, Inc. The 2008 Gallup Study of Concerns for Children's OTC Cold Medications. Multi-sponsor Surveys, Princeton, NJ, August 2008. (Data on file).

21. Forbes Consulting Group. RH Need States 2009. (Data on file).

22 . Barrett B, Brown R, Mundt M, et al. The Wisconsin Upper Respiratory Symptoms Survey is responsive, reliable, and valid. J Clin Epidemiol 2005;58:609-617.

SECTION 8 UNDERSTANDING ROOT CAUSES OF ACETAMINOPHEN OVERDOSE LEADING TO LIVER INJURY

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8 UNDERSTANDING ROOT CAUSES OF ACETAMINOPHEN OVERDOSE LEADING TO LIVER INJURY

8.1 Overview

In order to maximize effectiveness, potential interventions to reduce acetaminophen overdose and liver injury should be based upon and targeted to specific root causes of acetaminophen overdose. Analysis of root causes of acetaminophen overdose and liver injury by product type (OTC vs prescription, OTC single ingredient vs OTC combination ingredient), age (pediatric vs adult), intent (accidental unsupervised ingestion, therapeutic intent, self-harm), dose (overdose, reported therapeutic dose), and reasons for medication errors occurring with therapeutic intent provides insights for use in developing potential interventions. Where there are gaps or inconsistencies in the understanding of root causes of overdose and liver injury, McNeil supports additional research and enhanced surveillance.

8.2 Key Points

Review of cases from McNeil's post-marketing safety database reveal the following:

Product

- McNeil data are consistent with data from the ALF Study Group in that both OTC and prescription medicines contribute to acetaminophen overdose and liver injury.
- McNeil's data are consistent with data from the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) in that OTC combination ingredient acetaminophen containing medicines represent a small percentage of all cases.

Age

- McNeil's data are consistent with data from the ALF Study Group in that the vast majority of patients who develop liver injury are adults.

Intent

- Reported intent may not adequately characterize the actual intent of the patient at the time of acetaminophen exposure.

Pediatric Population

- McNeil's data are consistent with data from the AAPCC NPDS in that accidental unsupervised ingestions are an important root cause of acetaminophen exposures.
- Root causes of medication errors include administering greater than the labeled dose, administering concentrated infants' drops (100 mg/mL) at the dose of the childrens' suspension liquid (32 mg/mL), administering an adult medicine to a child, concomitant use of multiple OTC acetaminophen-containing medicines, and administering acetaminophen more frequently than labeled.

Adult Population

- McNeil's data are consistent with data from the AAPCC NPDS in that self-harm is the most frequently reported root cause of overdose and liver injury.
- Root causes of medication errors include taking greater than the labeled dose, concomitant use of prescription and OTC acetaminophen-containing medicines, concomitant use of multiple OTC acetaminophen-containing medicines, and taking acetaminophen more frequently than labeled.

Dose

- Reported dose ingested may not necessarily be the actual dose ingested.
- McNeil's data are consistent with the ALF Study Group in that most reports in children and adults involve reported overdose.

8.3 Introduction

This section provides the following:

- A root cause analysis of acetaminophen overdose cases from the McNeil commercial marketing adverse event reporting system.
- A review of intentionality data summarized by FDA including data from case reports/series and national databases including emergency room visits based on the National Electronic Injury Surveillance System, hospital discharge data from the National Hospital Discharge Survey, mortality data from the Multiple Cause of Death files, calls to poison centers from the National Poison Data System, and adverse event data from the FDA's Adverse Event Reporting System.
- McNeil's additional review of these databases and, when possible, updated information on intentionality.

8.4 Challenges with Assessing Intentionality

Data on the intention of consumers who take overdoses of acetaminophen may provide insights into possible preventive measures that may have an impact on reducing the number of acetaminophen overdoses. The impact of potential measure to reduce acetaminophen overdose may vary depending on the cause of the overdose. For example, a measure that may have an impact on intentional overdoses may have little effect on unintentional overdoses.

The coding of intentionality in relation to acetaminophen overdose presents some challenges. Intentionality has often been classified according to three categories: intentional, unintentional, and unknown intentionality. While this seems reasonable, there are several aspects of intentionality that introduce variability and inaccuracies into assigning these categories. For example, consider the patient who is hospitalized after intentionally taking repeat doses of multiple medicines containing acetaminophen or repeat doses of more than the recommended single dose of acetaminophen, but who is not intentionally trying to harm him- or herself. The hospital discharge diagnosis for such a patient could be coded as intentional acetaminophen poisoning (since the patient intentionally took more than recommended) or as an unintentional acetaminophen poisoning (since the patient did not intend self-harm). An example of unintentional acetaminophen overdose would be the patient who has no intention of misusing the medicine but who ingests more than the recommended dose or who unknowingly takes multiple acetaminophen products. However, identifying such patients presents difficulties since there are other factors that may lead to inaccurate patient reporting of dose and intentionality. These include the unwillingness of patients to admit product misuse for numerous reasons, ranging from avoiding the embarrassment of product misuse to financial and/or legal motivations to underreport dose. Similarly, the frequency of suicide as a reason for overdose may be higher than reported since suicidal intent is difficult to confirm. Disclosure of suicidal intent may be of concern given possible repercussions (eg, privacy, social stigma, and family impact).

Different databases use different criteria to develop categories for intentionality and more detailed categorization is not available from most databases. For example, the category of unintentional overdose usually includes acute accidental unsupervised ingestions leading to overdose as well as repeated supratherapeutic (chronic) ingestions leading to overdose, two overdose categories which likely require different potential solutions. In order to understand the root causes of acetaminophen overdose, subcategories of intention are useful, as demonstrated through use of AAPCC's NPDS subcategories of intention.

AAPCC subcategories of unintentional include therapeutic error, unintentional misuse, or unintentional unknown; subcategories of intentional include suicide, intentional abuse, intentional misuse, or intentional unknown; subcategories of other include contaminant/tampering, malicious, or withdrawal; adverse reaction is a separate category, as is unknown.

8.5 Root Cause Analysis of Adverse Event Data

8.5.1 Published Report of Emergency Room Data (NEISS)

In 2009, Willy et al (FDA) [1] reported on US emergency department (ED) visits for all ages attributed to selected analgesics during 2004 and 2005, based on data from NEISS. This analysis included allergic reactions, adverse effects at recommended doses, unintentional overdoses, and secondary effects (falls, choking). This analysis excluded cases of intentional self-harm, lack of therapeutic effect, drug withdrawal, drug abuse, and all adverse events that occurred as a result of treatment provided during the ED visit, and follow-up visits for a previously diagnosed adverse event. Analgesic use data from the Slone survey (2004 and 2005) were used in this analysis to estimate the weekly prevalence of analgesic use. ED visits for medications containing analgesics were estimated as 1.57 visits/100,000 users per week, with higher rates reported for those aged 0 to 9 years (4.88) and those 80 to 89 years (2.89). Estimates for specific analgesics were as follows: 2.05 for acetaminophen, 1.60 for naproxen, 1.07 for aspirin, and 0.71 for ibuprofen. Rates for acetaminophen were further classified as follows: 10.25 for narcotic-acetaminophen combinations, 0.87 for single-ingredient acetaminophen, and 0.62 for non-narcotic acetaminophen combinations. The most frequent type of adverse event leading to the ED visit varied by analgesic. Over all ages combined, for single-ingredient acetaminophen products and non-narcotic acetaminophen combination products, overdose was the most frequent type of adverse event, 70% and 39%, respectively. Many of these single-ingredient acetaminophen overdoses were in children. For narcotic-acetaminophen combination products and single-ingredient aspirin products, side effects were the most frequent type of adverse event, 46% and 49%, respectively. For ibuprofen products and naproxen, allergic adverse events were the most frequent type of adverse event, 47% and 64%, respectively. It was reported that 12% of ED visits resulted in hospitalization. The authors noted that the highest ED visit rate/100,000 users per week was for narcotic-acetaminophen combination products (10.25), and that nearly half of these visits were due to side effects.

8.5.2 Published Reports of Acute Liver Failure Study Group Data (ALFSG)

Larson et al [2] described 662 consecutive ALF patients at 22 tertiary care centers during the period 1998 to 2003. Of the 275 ALF cases considered to be associated with acetaminophen, 122 (44%) were classified as intentional overdose, 131 (48%) were classified as unintentional acetaminophen overdose, and intent was unknown in 22 cases (8%). Larson et al reported that the local site investigator assigned intentionality based on the patient's medical history as follows: intentional (suicidal) ingestion was defined as a single time point ingestion in a patient admitting suicidal intent, and unintentional ingestion was defined as a multiple time point ingestion to relieve pain or other somatic symptoms with denial of suicidal intent.

As shown in Figure 8-1, Larson et al reported that 53% of cases reported use of only OTC acetaminophen products, 28% reported use of only prescription opioid-acetaminophen combination products, and 15% reported use of both OTC acetaminophen and prescription opioid-acetaminophen combination products. Information was not reported for 4% of cases.

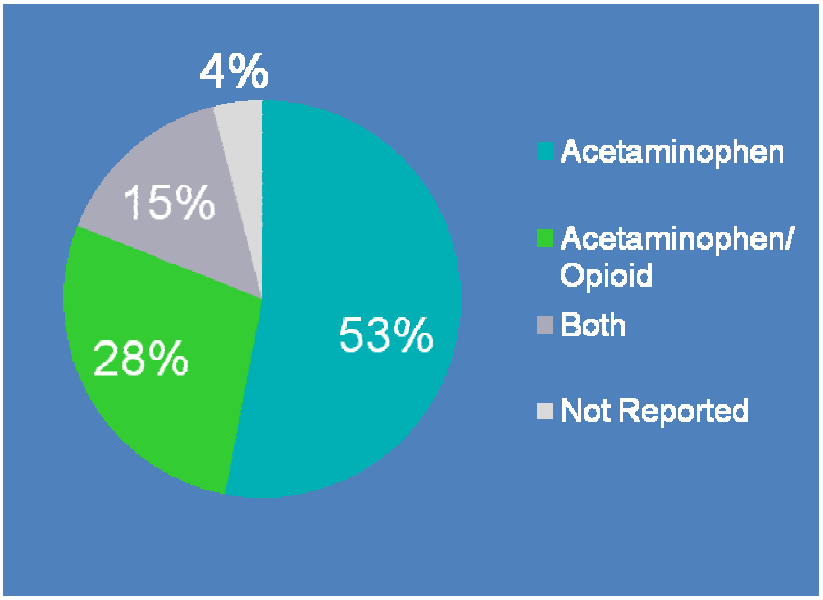

Figure 8-1. ALF Study Group Acetaminophen-Associated ALF Cases by Product Type (Data from Larson et al [2])

8.5.3 Company Post-marketing Database

The company post-marketing safety database was searched for the five-year period from January 1, 2004 through December 31, 2008 for cases from the United States and coded with a MedDRA (Medical Dictionary for Regulatory Activities) Preferred Term (PT) in the Standard MedDRA Query (SMQ) for Possible Drug Related Hepatic Disorders – Comprehensive Search with the following types of products: OTC Single-Ingredient and Combination–Ingredient acetaminophen products and Prescription Opioid-Acetaminophen products (ie, acetaminophen/codeine, acetaminophen/oxycodone, and acetaminophen/tramadol). The cases were manually reviewed and categorized according to product (OTC and prescription, OTC single ingredient and OTC combination ingredient), age (adult and pediatric <12 years) intent (ie, accidental unsupervised ingestion, therapeutic, self-harm, unknown), seriousness of the reported 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.

Section 8.5.3.1 summarizes data for adults and children ≥ 12 years of age and Section 8.5.3.2 summarizes data for children < 12 years of age.

Figure 8-2 provides an overview of the methodology used for the root cause analysis of cases and Figure 8-3 summarizes the terminology for describing overdose.

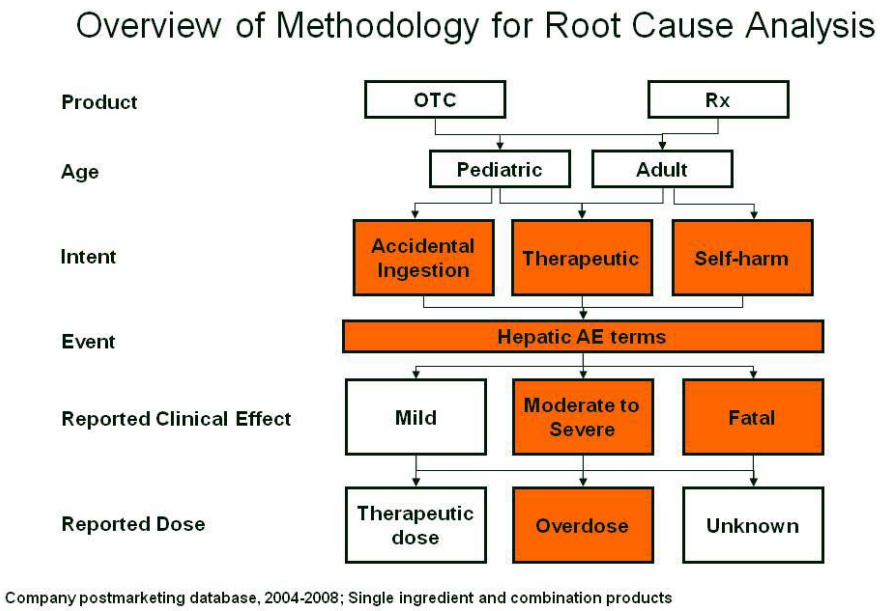

Figure 8-2. Overview of Methodology for Root Cause Analysis

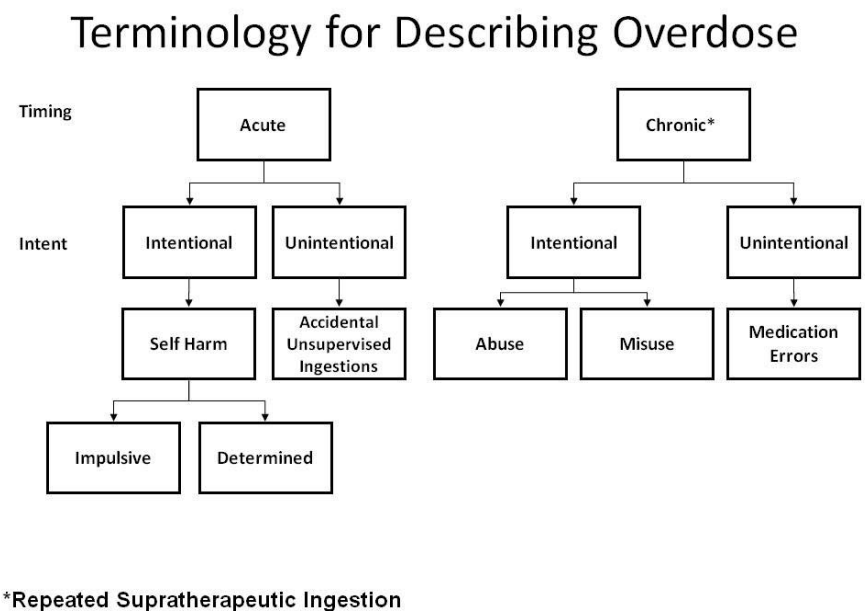

Figure 8-3. Terminology for Describing Overdose

8.5.3.1 Adults and Children ≥ 12 Years of Age

8.5.3.1.1 OTC Single- and Combination-Ingredient Acetaminophen Medicines

Of all overdose cases reported in adults and children ≥ 12 years of age with single- and combination-ingredient OTC acetaminophen products, self-harm was the most frequently reported cause of overdose. Of the cases reporting moderate to severe or fatal hepatic effects with therapeutic intent, medication error was identified as the root cause of overdose. Of the medication error reports, approximately 50% were reported to involve taking greater than the labeled dose of acetaminophen, approximately 20% were reported to involve use of prescription and OTC acetaminophen-containing medicines, nearly 15% were reported to involve simultaneous use of multiple OTC acetaminophen-containing medicines, and approximately 10% were reported to involve taking the medicine more frequently than labeled. The cases reported as medication errors could appear in multiple subcategories.

8.5.3.1.2 Prescription Opioid-Acetaminophen Medicines

Of the cases identified in adults and children ≥12 years of age with a preferred term in the SMQ for Possible Drug Related Hepatic Disorders – Comprehensive for the prescription opioid-acetaminophen products (ie, acetaminophen/codeine, acetaminophen/oxycodone, and acetaminophen/tramadol), approximately one-third reported self-harm, and approximately one-third reported therapeutic intent. The remaining cases either reported intentional misuse or did not specify intent. Of the few cases reporting moderate to severe or fatal hepatic effects with therapeutic intent, all specified a medication error as the root cause of overdose. Of these medication error reports, approximately 30% (n=1) indicated taking greater than the labeled dose of acetaminophen and approximately 70% (n=2) reported simultaneous use of prescription and OTC acetaminophen containing products.

8.5.3.2 Pediatric Safety Data – Children < 12 Years of Age

8.5.3.2.1 OTC Single- and Combination-Ingredient Acetaminophen Medicines

Of all cases reported in children < 12 years of age, accidental unsupervised ingestion accounted for 24% of the cases. Only 1% of these cases reported a preferred term in the 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. Of the cases reporting moderate to severe or fatal hepatic effects with therapeutic intent, medication error was identified as the root cause of overdose. Of

the cases describing medication errors, approximately 40% were reported to involve administration of greater than the labeled dose of acetaminophen, approximately 30% were reported to involve administering the concentrated infants drops (100 mg/mL) at the dose of the children's suspension liquid (32 mg/mL), approximately 20% were reported to involve administering an adult product to a child, approximately 20% were reported to involve simultaneous use of multiple acetaminophen-containing products, and approximately 10% were reported to involve administering the medicine more frequently than labeled. A few of the cases reported as medication errors had multiple root causes of overdose identified and are counted in more than one subcategory.

8.5.3.2.2 McNeil's Survey to Determine the Root Cause of Pediatric Accidental Unsupervised Ingestions

To explore the root causes of accidental unsupervised ingestions (AUIs), McNeil Consumer Healthcare conducted a retrospective case review of US reports in children <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. In this review, cases were included with the following MedDRA terms (accidental drug intake by child, accidental exposure, accidental overdose and failure of child resistant (CR) mechanism) over approximately 1/3 year (Q3 2008-Q1 2009). Healthcare professionals in McNeil's Medical Affairs department called reporters to obtain additional information about the reported accidental ingestion and how caregivers normally store medications in their home using a survey that McNeil developed in conjunction with healthcare providers from four US Poison Centers.

Two hundred twenty reports met the criteria for inclusion. One hundred seventy five caregivers were not able to be contacted due to various reasons such as: they could not be reached, no phone number was provided during original call, patient refused to give permission to be contacted, telephone number had been disconnected or reporter had moved, or caregiver hung up. Forty-five (20%) caregivers completed the survey.

All of the AUIs occurred in children <7 yrs of age; 78% of the AUIs occurred in children 1 to <4 yrs of age. Fifty-six percent of the AUIs occurred in males and 80% of the ingestions were unobserved by the caregiver. Eighty-nine percent of ingestions occurred at the primary residence with 36% of the ingestions occurring in the bedroom; 33% in the kitchen and 13% in both the living room and bathroom. Approximately 50% of the time the medicine was out of the child's immediate reach but the child accessed the medicine by

climbing on an object (eg, stool, books, toys). For 71% of the cases, the caregiver was in a different room at the time of the AUI.

The medicine was intended for the child who accidentally ingested the medicine for 56% of the cases and for 44% of cases it was intended for someone else (40% parent, 30% sibling, 15% grandparent). The majority of caregivers (76%) reported storing their medicines in a high out of sight area when not in use; however 60% of the reported AUIs occurred when medicines were not in their normal storage area. More than half (67%) of the caregivers reported storing prescription and OTC medicines in the same place and 64% reported storing adult and pediatric medicines in the same place. Most caregivers (76%) reported storing medicines in multiple rooms of their house with 84% storing in at least two rooms.

Almost 50% of the time, the ingestion occurred within 1 day of the last time the caregiver had administered a therapeutic dose of the medicine to the child.

In summary, McNeil's survey showed that most of these reported AUIs with OTC medicines occur at home, in the bedroom or kitchen and are unobserved when the caregiver is in a different room. Pediatric formulations intended for use by child who had an AUI are commonly involved. Although most caregivers store medicines in a high area out of sight, AUIs often occur within 24 hours of the last therapeutic dose when the OTC medicine is not in its normal storage location. Medicines are commonly stored within multiple rooms and not in a locked location. Caregivers store OTC and adult medicines differently than prescription and pediatric medicines. New insights into root causes of AUI's may help guide targeted interventions and educational efforts.

8.6 Summary of Databases Assessing Intentionality of Acetaminophen Overdose

FDA has summarized consumer intention with acetaminophen-associated liver injury using several databases [3]. These databases provided information on emergency room visits, hospitalizations, mortality, poison center calls, and reports of adverse events. A discussion of each source of data is provided in the following sections, including a description of the limitations of the databases and for certain databases, a review of McNeil's additional analyses. These databases provide estimates of the percentage of acetaminophen-associated events that were intentional (41% to 74%), unintentional (8% to 50%), and of unknown intent (5% to 20%).

8.6.1 National Electronic Injury Surveillance System (NEISS)

The NEISS collects information on consumer product-related injuries treated in emergency departments (EDs) of 100 hospitals selected as a probability sample of the over 5000 US hospitals with EDs [4]. Data collected by NEISS helps Consumer Product Safety Commission analysts make timely national estimates of the number of injuries associated with (not necessarily caused by) specific consumer products [4]. FDA's review included an analysis for the period January 2000 to June 2001 and included an assessment of intentionality based on a review of the text in comment fields for selected product names [3]. Suicide or suicidal gestures were included as intentional overdoses. Unintentional overdoses included those in children less than five years of age and those overdoses that were therapeutic errors. All other acetaminophen overdoses were categorized as unknown/other intent. Based on data from 2001, FDA estimated that 56% of acetaminophen-associated overdoses that led to ED visits were intentional, 23% were unintentional, and 20% were of unknown intent.

In the 2006 Nourjah paper, it appears that a large majority of the ED visits associated with unintentional acetaminophen overdose occurred in children. Since only 23% of all ED visits in the NEISS data were reported to be from unintentional overdose, it appears likely that the vast majority (17/23 or 74%) of unintentional overdose ED visits were by children less than six years of age [3]. Acetaminophen overdoses in children this young are most likely unintentional, resulting either from medication errors by parents or other caregivers, or failure to restrict access of acetaminophen to children (Accidental Unsupervised Ingestion). An additional 16% of ED visits were for children six to 16 years of age, and an unknown fraction of these are also likely related to unintentional overdose. Thus, almost all ED visits reported in the NEISS database related to unintentional overdoses occurred in children, most likely accidental unsupervised ingestions.

8.6.2 National Hospital Discharge Survey (NHDS)

The NHDS is a probability survey sample of patient discharge records from non-Federal, short stay hospitals in the US. Intentionality of acetaminophen overdose is based on ICD-9 codes reported on the patient discharge record. Based on data collected from 1990 to 1999, FDA estimated that acetaminophen overdose was associated with an annual average of 26,256 hospitalizations [3]. Intentional acetaminophen overdoses included those with poisoning by drugs, medicinal, and biological substances (ICD-9 codes of 960.0 through 965.3 and 965.5 through 979.9). In addition, acetaminophen overdoses with suicide and self-inflicted injury (external cause of injury codes of E850.0 through 850.3 and E850.5 through 858.9) were included as intentional overdoses. Unintentional overdoses included

accidental poisoning by drugs, medicinal, and biologicals – aromatic analgesics, not elsewhere classified (coded as E850.4) without depressive disorder (ICD-9 codes of 309.0-309.1, 311, 301.12, 301.13, 300.4, 298.0, 296.2, 296.3, 296.5, 296.6, 296.8, 308.0, or 313.1). All other hospitalizations with acetaminophen overdose were categorized as unknown/other intent. Nourjah reported that 74% of hospitalizations with acetaminophen overdose were intentional, 8% were unintentional, and 17% were of unknown intention. Event rates using population estimates and trends over time were not reported by FDA.

This database includes a large number of pediatric hospitalizations, as well as readmissions for the same diagnosis. It appears that many of the hospitalizations associated with unintentional acetaminophen overdose occurred in children.

McNeil has obtained and reviewed data for the period 2000 through 2006. During this period, 74% of hospitalizations with acetaminophen overdose were intentional 9% were unintentional, and 17% were of unknown/other intent. These estimates are consistent with FDA's estimates for 1990 to 1999.

8.6.3 Multiple Cause of Death (MCOD) Files

The Multiple Cause of Death Files is a database that contains information from death certificates. FDA analyzed data from the years 1996 to 1998 [3]. Cases with ICD-9 codes for acetaminophen overdose as an underlying or contributing cause of death were included in the analysis; these codes included 965.4 (poisoning by acetaminophen) and E850.4 (accidental acetaminophen poisoning). FDA estimated that an average of 458 deaths/year were at least in part attributable to acetaminophen overdose. Intentional acetaminophen overdoses included poisoning by drugs, medicinal, and biological substances (ICD-9 codes of 960.0 through 965.3 and 965.5 through 979.9). In addition, acetaminophen overdoses with suicide and self-inflicted injury (external cause of injury codes of E850.0 through 850.3 and E850.5 through 858.9) were included as intentional overdoses. Unintentional overdoses included accidental poisoning by drugs, medicinal, and biologicals – aromatic analgesics, not elsewhere classified (coded as E850.4) without depressive disorder (ICD-9 codes of 309.0-309.1, 311, 301.12, 301.13, 300.4, 298.0, 296.2, 296.3, 296.5, 296.6, 296.8, 308.0, or 313.1). All other deaths with acetaminophen overdose were categorized as unknown/other intent. Nourjah reported that 74% of deaths with acetaminophen overdose were intentional, 22% were unintentional, and 5% were of unknown intention.

McNeil reviewed acetaminophen-associated mortality rates for all ages by intentionality for the years 1999 through 2006 from the national multiple cause of death files. In 1999, the use of ICD-10 codes was initiated for US mortality data. An ICD-10 code of T39.1 (4-aminophenol derivatives) was used to identify acetaminophen poisoning as a contributing cause of death. Acetaminophen poisoning deaths with a contributing cause of death code of X60 (intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics) were counted as intentional. Acetaminophen poisoning deaths with a contributing cause of death code of X40 (accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics) were counted as unintentional. Acetaminophen poisoning deaths with a contributing cause of death code of Y10 (poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent) were counted as unknown intention. Acetaminophen-associated mortality rates were stable for the years 1999 through 2006. During this longer assessment period, 41% of acetaminophen-associated deaths categorized as drug poisoning deaths were also categorized as intentional, 49% as unintentional, and 10% as unknown intention.

8.6.4 National Poison Data System (NPDS)

The National Poison Data System (formerly the Toxic Exposure Surveillance System) is a database of all human (pediatric and adult) exposures reported to over 60 US poison centers. Case reporting is not mandatory and is based on callers requesting information from poison control centers. FDA's review by Nourjah [3] reported that there were 119,807 acetaminophen exposures alone or in combination with other products reported in 1997; this number declined to 112,809 reports in 2001. Suicides were included as intentional overdoses. Unintentional overdoses included those overdoses that were therapeutic errors, intentional misuse, and unintentional overdoses with unknown further categorization. All other acetaminophen overdoses were categorized as unknown/other intent. Nourjah reported that in 2001 nearly 50% of all acetaminophen exposures reported were unintentional; 173 acetaminophen-associated fatalities occurred, of which 55% were reported to be intentional and 26% were unintentional.

It is important to note that the Nourjah analysis included pediatric cases. The percentage of NPDS reports that are unintentional is much lower for adults, ie, 25%. It is also important to note that calls to poison centers are for events of varying severity, including many events that may not rise to the level of overdose. In addition, NPDS categorizes the reasons for drug exposure as: (1) unintentional (therapeutic error, unintentional misuse, or unintentional unknown); (2) intentional (suicide, intentional abuse, intentional misuse, or intentional

unknown); (3) other (contaminant/tampering, malicious, or withdrawal), (4) adverse reaction, and (5) unknown. Nourjah et al included only suicide in their intentional category, and grouped intentional misuse with therapeutic error and unintentional misuse in their unintentional category; intentional abuse, intentional unknown, and unknown were combined in the 'other' category.

8.6.5 Adverse Event Reporting System (AERS)

AERS, FDA's surveillance system of voluntary post-marketing adverse event reports, contains reports submitted by manufacturers as well as by health care professionals and consumers. AERS data presented at the 2002 NDAC meeting were summarized by FDA for the period from January 1998 through July 2001 [71 FR 377314 at 77320-21]. Six hundred thirty-three (633) reports were identified and after excluding duplicates and apparent suicidal attempts, 25 pediatric and 282 adult cases, presumably unintentional, remained.

In FDA's review by Nourjah [3], AERS reports of hepatotoxicity associated with the use of acetaminophen products in individuals 12 years of age and older between 1998 and 2001 were described. Suicide attempts were considered to be intentional overdoses as well as cases in which a one-time dose of acetaminophen greater than four grams without a specified indication was reported. Unintentional cases included those with use of acetaminophen for a therapeutic indication, or misuse or abuse, if suicide attempt was not indicated. Unknown intention included those cases with unspecified intentionality. No inferences were made for cases with a history of depression. Overall, 42% of AERS cases of acetaminophen-associated overdoses were categorized as intentional, 41% as unintentional, and 17% as unknown/other intent. Of the 478 cases of serious hepatotoxicity identified, 200 were categorized as apparent suicides, 198 as unintentional, and 80 were of unknown intent. Of the 198 unintentional cases, 103 provided information to estimate daily acetaminophen dose, with 73 of the 103 exceeding 4 g/day. Fifty-five (55) of the 103 cases reported use of more than one acetaminophen product, often an OTC product and a prescription narcotic-acetaminophen product. A therapeutic indication, usually analgesia, was the reason for use for 170 unintentional cases; 89 of these unintentional cases had dose information and a mean daily dose of 7.5 g was estimated. Alcohol use and prior liver disease were noted for 44 and 29 unintentional cases, respectively.

8.7 Reference List

1. Willy M, Kelly J, Nourjah P, et al. Emergency department visits attributed to selected analgesics, United States, 2004-2005. Pharmacoepidemiol Drug Saf 2009;18:188-195.
2. Larson AM, Polson J, Fontana RJ, et al. Acetamiophen-induced actue liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-1372.
3. Nourjah P, Ahmad SR, Karwoski C, et al. Estimates of acetaminophen (paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 2006;15:398-405.
4. Consumer Product Safety Commission. National Electronic Injury Surveillance System. Available at: http://www.cpsc.gov/cpscpub/pubs/3002.html Accessed April 30, 2007.

SECTION 9 ESTIMATES AND CONSEQUENCES OF SWITCHING FROM ACETAMINOPHEN TO NSAIDS

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9 ESTIMATES AND CONSEQUENCES OF SWITCHING FROM ACETAMINOPHEN TO NSAIDS

9.1 FDA's Areas of Concern

FDA has proposed six options in the document titled, Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury, included in FDA's May 22, 2009 background package for the June 29-30, 2009 joint advisory committee meeting. FDA states in its considerations related to incidence of hepatotoxicity (liver injury) under Option 1A (reduce current dosage strengths) that if consumers feel that the proposed maximum recommended dose of 650 mg is ineffective, they could respond by "Switching to alternative treatments, such as NSAIDs, thus reducing the incidence of overdose, but potentially increasing incidence of NSAIDs-related side effects." Similarly, FDA states in its considerations related to incidence of hepatotoxicity (liver injury) under Option 2 (establish package size limits) that "Limiting the availability of acetaminophen could move consumers to use other analgesics to treat pain with their attendant risk of adverse effects."

9.2 Key Points

- The potential for and the consequences of patients and consumers switching to other OTC analgesics should be considered when evaluating options to reduce acetaminophen overdose.
- Elimination of the acetaminophen 1000 mg dose will likely drive current acetaminophen users to NSAID use.
- Available data suggest that switching from use of acetaminophen to NSAIDs may result in more people dying from NSAID-associated gastrointestinal bleeding and renal failure than those potentially spared from acetaminophen-associated liver injury.

9.3 Introduction

It is important to consider the unintended public health consequences of potential changes in acetaminophen availability, given that OTC analgesics are used on a frequent basis and by a large percentage of the US population. In particular, the potential for switching from acetaminophen use to NSAID use and the consequences of switching needs to be considered.

9.4 Eliminating the Acetaminophen 1000 mg Dose Will Likely Drive Switching to NSAIDs

Although the number of clinical trials that have directly compared acetaminophen 1000 mg to acetaminophen 650 mg is relatively small, the majority demonstrate additional effectiveness with the higher dose. In addition, meta-analyses show that a greater number of subjects achieve pain relief with acetaminophen 1000 mg compared to acetaminophen 650 mg. Furthermore, pharmacokinetic-pharmacodynamic modeling demonstrates that acetaminophen 1000 mg yields significant peak plasma concentrations that consistently meet or exceed the EC_{50}, the concentration in the effect compartment that elicits 50% of the maximum drug response, whereas acetaminophen 650 mg does not. Taken together, these data clearly support that acetaminophen 1000 mg provides more analgesia than acetaminophen 650 mg. These data are described in more detail in Section 3, Efficacy and Safety of Acetaminophen.

As described in Section 3.7.3.2, McNeil and J&J PRD Meta-Analysis, data from McNeil's meta-analysis comparing the efficacy of acetaminophen 1000 mg to acetaminophen 650 mg provided NNTs of 9.2 (indirect comparison) and 22 (direct comparison). These NNTs suggest that 4.5% (based on an NNT of 22) and 11% (based on an NNT of 9.2%) of patients using acetaminophen would benefit from 1000 mg but not from 650 mg. Applying these percentages (4.5% and 11%) to the 18% of the population using acetaminophen in any given week, suggests that 0.8% (1.8 million people) to 2.0% (4.4 million people) of the adult US population in any given week would benefit from the higher acetaminophen dose.

While lower doses of acetaminophen (650 mg and 500 mg) are effective for some individuals, others require a higher dose (1000 mg) to achieve adequate analgesia. Two studies [1,2] demonstrated that acetaminophen 1000 mg was statistically significantly superior to acetaminophen 650 mg for analgesia in subjects with severe, but not moderate, initial pain. Based on data from the NHAMCS survey [3], of the 119 million patients who presented to the emergency room in 2006, approximately 16 million had mild pain, 30 million had moderate pain, and 24 million had severe pain. Data on pain

severity in the US are also available from a national survey of pain in America conducted by ABC News, USA Today, and the Stanford University Medical Center through a telephone poll (April 13-19, 2005) among a random national sample of 1204 adults. In this survey, 37% of those who reported pain categorized their pain as mild, 42% as moderate, and 20% as severe [4]. Additionally, in a mail questionnaire survey (n=1456 respondents) of pain and treatment behavior conducted in September and October 2004 using a daily log of pain behavior for two consecutive weeks, 16% of respondents with pain reported that they had little pain, 51% reported moderate pain, and 34% reported severe pain [5]. Treatment of pain was reported by 19% of respondents with little pain, 48% of those with moderate pain, and for 72% of those with severe pain.

If the maximum individual dose of acetaminophen available is reduced to 650 mg, it is likely that those individuals that do not achieve adequate analgesia with this dose (ie, those with more severe pain), will take one of two actions. First, they could decide to take an additional dose, which could be either 325 mg or 650 mg. In either case, they would effectively be using near or above the currently allowed maximum dose of 1000 mg. Secondly, they could switch to NSAIDs in an effort to obtain adequate analgesia. One could conservatively estimate that 20% of patients and consumers, ie, those with severe pain, would switch to other analgesics (NSAIDs) if acetaminophen 1000 mg were not available. This estimate is conservative based on the likelihood of ibuprofen 400 mg demonstrating superiority to acetaminophen 650 mg and these data supporting a large marketing campaign to increase ibuprofen sales. It is likely that the percentage of acetaminophen users switching to NSAIDs would be much higher, possibly 50% to 75%. The impact of these rates of switching is described in Section 9.5, Impact of Switching on Adverse Events.

A consumer seeking pain relief or fever reduction should not be denied the opportunity to use the most effective dose of acetaminophen that is appropriate for the individual consumer's circumstances and needs, when it has been demonstrated that acetaminophen can be safely used at the individual dose of 1000 mg as well as up to the maximum labeled daily dose of 4000 mg.

9.5 Impact of Switching on Adverse Events

McNeil commissioned an analysis by IEI of the possible effects on deaths from adverse events due to switching from use of acetaminophen to NSAIDs. IEI developed a switching model and evaluated effects with 10% switching and 20% switching [6]. Increases in the numbers of deaths associated with gastrointestinal bleeding and acute renal failure were considered as well as decreases in the number of deaths associated

with acetaminophen poisoning and acute liver failure. The details of the switching model associated with each of these changes are described in the sections that follow, followed by an overall summary of these changes.

9.5.1 Increases in NSAID-Associated Gastrointestinal Bleeding

Significant morbidity and mortality are associated with chronic use of NSAIDs. As cited in FDA background materials (Recommendations from the Acetaminophen Hepatoxicity Working Group, page 9), it has been estimated that NSAIDS may account for nearly 34% of all gastrointestinal bleeding cases in the US, resulting in 3,200 deaths and 32,000 hospitalizations each year [7]. McNeil consulted with the authors of this publication (Tarone et al) to obtain updated estimates using the methodology as previously reported. It is understood that other methodologies could be used for this purpose and may result in variations in estimates, but in general the results and interpretation would likely be similar.

Estimating the increase in numbers of deaths due to gastrointestinal bleeding associated with NSAIDS requires the use of estimates of relative risk of gastrointestinal bleeding among NSAID users, the prevalence of NSAID use and acetaminophen use, and an estimate of the percentage of acetaminophen users switching to NSAID use. A four-fold or slightly higher increase in relative risk of gastrointestinal bleeding among current NSAID users has been generally reported in most observational epidemiologic studies [7]. However, a slightly lower relative risk of 3.7 for current NSAID use was reported in a recent publication of NSAID use and gastrointestinal complications [8]. Based on interviews of 3,276 US subjects older than 15 years of age during the period January 2006 through May 2007, the weekly prevalence of NSAID use was 22% [Slone 2009, personal communication].

The percentage of gastrointestinal bleeding deaths attributable to NSAID use was estimated as (RR-1)×P ÷ [1 + (RR-1))×P], where P denotes the prevalence of NSAID use and RR denotes the relative risk of gastrointestinal bleeding associated with NSAID use. Using a conservative estimate of 3.5 for the relative risk of gastrointestinal bleeding associated with NSAID use and an estimated prevalence of any NSAID use of 22%, the percentage of gastrointestinal bleeding events associated with NSAID use was estimated to be 35.5%. Accordingly, using national multiple cause of death files and based on the 9,150 deaths in 2006 with gastrointestinal bleeding listed as the underlying cause of death [ICD-10 codes of K92.2 (gastrointestinal hemorrhage, unspecified); K29.0 (acute hemorrhagic gastritis); K25.0, K25.2, K25.4, and K25.6 (bleeding associated with gastric ulcer); K26.0, K26.2, K26.4, and K26.6 (bleeding associated with duodenal ulcer); K27.0, K27.2, K27.4, and K27.6 (bleeding associated with peptic ulcer);

and K28.0, K28.2, K28.4, K28.6 (bleeding associated with gastrojejunal ulcer], it was estimated that NSAIDs contribute to 3,247 deaths annually in the United States with gastrointestinal bleeding as the underlying cause of death.

The Slone Survey determined that 18% of people in the US used acetaminophen each week [Slone 2009, personal communication]. If 10% of acetaminophen users switch to NSAID use, then the increase in NSAID-associated gastrointestinal bleeding events was estimated by adding 1.8% (10% of 18%) to the estimated prevalence of NSAID use in the formula previously provided for estimating the percentage of gastrointestinal bleeding attributable to NSAID use. Accordingly, using an estimated prevalence of use for NSAIDs of 23.8%, it was estimated that there would be 166 additional deaths per year with gastrointestinal bleeding as the underlying cause of death resulting from a switch of 10% of acetaminophen users to NSAID use. Similarly, a switch of 20% of acetaminophen users to NSAID use would increase the prevalence of NSAID use by 3.6% (ie, to 25.6% prevalence of NSAID use), and result in an estimated 324 additional deaths per year with gastrointestinal bleeding listed as the underlying cause of death. These estimates are summarized in Table 9-1.

9.5.2 Increases in NSAID-Associated Acute Renal Failure

A process similar to that used for gastrointestinal bleeding was used to estimate changes in deaths due to NSAID-related renal failure. Recent studies reported relative risks for acute renal failure and current NSAID use of 3.2 [9] and 2.3 [10]. A relative risk of 2.5 was used to estimate the additional number of acute renal failure deaths due to switching from acetaminophen use to NSAID use. Based on a relative risk of 2.5 and an estimate of 22% for the prevalence of NSAID use, the percentage of acute renal failure events associated with NSAID use was estimated to be 24.8%. Since 7,612 deaths in 2006 had acute renal failure (ICD-10 code N17) listed as the underlying cause of death, it follows that an estimated 1,889 acute renal failure deaths are caused per year by NSAID use.

The estimated additional number of acute renal failure deaths due to switching from acetaminophen to NSAID use was calculated in the same manner as for gastrointestinal bleeding. If 10% of acetaminophen users switch to NSAIDS there would be a 1.8% increase in the prevalence of NSAID users, which would result in estimates of 114 additional deaths per year with acute renal failure listed as the underlying cause of death. Similarly, if 20% of acetaminophen users switch to NSAIDs there would be a 3.6% increase in the prevalence of NSAID users, which would result in estimates of 223 additional deaths per year with acute renal failure listed as the underlying cause of death. These estimates are summarized in Table 9-1.

9.5.3 Decreases in Acetaminophen Poisoning and Acute Liver Failure

In order to estimate the decrease in the number of acetaminophen-poisoning deaths that would result from switching from acetaminophen use to NSAID use, an estimate of the maximum likely annual number of deaths that could possibly have been caused by acetaminophen poisoning was calculated. This maximum number of deaths was defined using underlying cause of death (UCOD) and contributing cause of death (CCOD) and included all deaths with an ICD-10 code of T39.1 (4-aminophenol derivatives) in combination with any of the following codes: X40 (accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics) as an UCOD; X60 (intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics) as an UCOD; Y10 (poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent) as an UCOD; acute liver failure [K72.0 (acute and subacute liver failure), K72.9 (hepatic failure, unspecified), K76.7 (hepatorenal syndrome), K71.9 (toxic liver disease, unspecified), K75.9 (inflammatory liver disease unspecified), and K76.9 (liver disease, unspecified)] as an UCOD or CCOD. There were 350 such deaths in 2006. This is likely an overestimate of the number of deaths actually caused annually by acetaminophen in the US, because acute liver failure was not listed as either the underlying or a contributory cause of death for over 40% of these deaths. However, using the estimate of 350 deaths per year, if a switch of 10% of acetaminophen users to NSAIDs results in a 10% decrease in acetaminophen-associated deaths, then there would be 35 fewer such deaths each year. Similarly, a 20% decrease in acetaminophen users would result in 70 fewer acetaminophen poisoning deaths per year.

Additionally, a subset of the acetaminophen-poisoning deaths, acetaminophen-associated deaths that included acute liver failure as an underlying or contributing cause of death were also estimated. As described above, acetaminophen-associated deaths were defined as any death with an ICD-10 code of T39.1 (4-aminophenol derivatives); deaths from acute liver failure included deaths with IDC-10 codes of K72.0, K72.9, K76.7, K71.9, K75.9, and K76.9. Using multiple cause of death files from 2006, there were 198 deaths in the US associated with acetaminophen and acute liver failure, resulting in the estimated annual mortality rate of 0.66 per million. In addition, a recent population based study of eight counties in Metropolitan Atlanta indicated an annualized incidence of acute liver failure for all causes of 5.5 per million people [11]. Since 40% of the acute liver failure cases were determined to be associated with acetaminophen, the annual incidence rate of acetaminophen-associated acute liver failure was estimated as 2.2 per million. Applying ALF Study Group case fatality rates of 28% [12] to the 2.2 per

million yields an estimated annual mortality rate for acetaminophen-associated acute liver failure of 0.62 per million, an estimate quite similar to the 0.66 per million estimated using national multiple cause of death files. This corresponds to approximately 200 deaths from acetaminophen-associated acute liver failure in the US each year. If a switch of 10% of acetaminophen users to NSAIDs results in a 10% decrease in acute liver failure deaths, then there would be 20 fewer such deaths each year. Similarly, a 20% decrease in acetaminophen users would result in 40 fewer acute liver failure deaths per year.

9.5.4 Summary of Changes in Analgesic-Associated Deaths

Table 9-1 summarizes estimated annual changes in the numbers of analgesic-associated deaths with acetaminophen users switching from use of acetaminophen to NSAIDs. While the table provides estimates for both acetaminophen poisonings and acute liver failure, for the comparisons that follow only the estimates for acetaminophen poisoning will be used since these estimates also include the acute liver failure estimates. The estimated numbers of acetaminophen-poisoning deaths prevented each year (35 and 70 for 10% and 20% switching, respectively) are 13% of the estimated total numbers of additional deaths caused by increased NSAID use in which gastrointestinal bleeding and acute renal failure are the underlying cause of death (280 and 547 for 10% and 20% switching, respectively). Overall, if 10% of acetaminophen users switch to NSAIDS, it is estimated that there would be an additional 245 deaths each year due to analgesics; with 20% switching there would be an additional 477 deaths each year.

Table 9-1. Estimated Annual Change in Number of US Deaths with Switching From Acetaminophen to NSAIDs

	Percent Switching	
Adverse Event Associated with Death	10%	20%
Gastrointestinal bleeding[a]	+166	+324
Acute renal failure[a]	+114	+223
Acetaminophen poisoning[b]	-35	-70
Acute liver failure[b]	-20	-40
Total[c]	+245	+477

a: Underlying cause of death
b: Underlying or contributing cause of death
c: Total change in deaths includes estimates for gastrointestinal bleeding deaths, acute renal failure deaths, and acetaminophen poisoning deaths (since acute liver failure deaths are also included in the acetaminophen poisoning deaths)

9.6 Conclusions

- The potential for and the consequences of patients and consumers switching to other OTC analgesics should be considered when evaluating options to reduce acetaminophen overdose.
- Elimination of the acetaminophen 1000 mg dose will likely drive current acetaminophen users to NSAID use.
- Available data suggest that switching from use of acetaminophen to NSAIDs may result in more people dying from NSAID-associated gastrointestinal bleeding and renal failure than those potentially spared from acetaminophen-associated liver injury.

9.7 Reference List

1. McNeil Consumer Healthcare Clinical Study Report for Protocol 0-223: A double-blind, single dose evaluation comparing the analgesic efficacy and adverse effect liability of acetaminophen 650 mg, acetaminophen 1000 mg, and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, March 1982 (data on file).

2. McNeil Consumer Healthcare Clinical Study Report for Protocol 0-214: A double-blind, single dose evaluation comparing the analgesic efficacy and adverse event liability of acetaminophen 650 mg, acetaminophen 1000 mg, and placebo in the treatment of postoperative pain following oral surgery. Fort Washington, PA: McNeil Consumer Healthcare, July 1981 (data on file).

3. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. National health statistics reports; no 7. Hyattsville, MD: National Center for Health Statistics. 2008.

4. ABC News/USA Today/Stanford University Medical Center. Poll: Americans searching for pain relief. Accessed online June 3, 2009 at http://abcnews.go.com/print?id=732395

5. Alcott Group. Pain & Body Need States. 2004 (data on file).

6. IEI report. Tarone R, Mumma M, Blot W, et al Analyses of U.S. multiple-cause-of-death tapes from 1999 through 2006, with estimated changes in the numbers of deaths caused by analgesic-associated adverse events if acetaminophen users switch to NSAID use. June 2009 (data on file).

7. Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther 2004;11:17-25.

8. Garcia Rodriguez LA, Tolosa LB. Risk of gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterol 2007;132:498-506.

9. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis 2005;45:531-539.

10. Schneider V, Levesque LE, Zhang B, et al Association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure: a population-based, nested case-control analysis. Am J Epidemiol 2006;164:881-889.

11. Bower WA, Johns M, Margolis HS, et al Population-based surveillance for acute liver failure. Am J Gastroenterol 2007;102:2459-2463.

12. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-1372.

SECTION 10 CONSUMER NEED AND MEDICAL BENEFIT FOR ACETAMINOPHEN

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10 CONSUMER NEED AND MEDICAL BENEFIT FOR ACETAMINOPHEN

10.1 Key Points

- In the United States (US), acetaminophen-containing products (over-the-counter [OTC] and prescription) are among the most frequently used medications. In any given week, some 19-23% of adults report using acetaminophen-containing products; recent medication use surveys suggest that the vast majority of consumers report using acetaminophen within the labeled OTC daily dose.
- Conditions commonly treated with acetaminophen include joint pain/stiffness, back pain, acute pain, headache, neck/shoulder pain, and muscle aches and pains.
- Acetaminophen is the most commonly recommended OTC analgesic in the US. Physicians recommend acetaminophen more commonly than ibuprofen and aspirin for numerous indications, including cold/flu, non rheumatoid arthritis, traumatic pain, post-surgical pain, and headaches. Additionally, acetaminophen is recommended as the OTC analgesic of choice for specific subpopulations at risk for nonsteroidal anti-inflammatory drug (NSAID)-associated gastrointestinal, cardiovascular, or renal adverse effects.

10.2 Consumer Use of Acetaminophen

10.2.1 2008 TNS Ailment Diary

TNS Ailment Diary is an online interactive panel of a nationally representative sample of US households. Each 4-week period, 800 randomly sampled households from the panel are selected to complete a 4-week daily diary. Information is collected for up to 10 members in each household. Each week, respondents report all symptoms experienced and any treatment (medical, alternative or non-medical) used by any household member. In addition, any OTC or prescription medication taken for preventative purposes is reported. The 2008 TNS Ailment Diary data [1], which includes data from 11,473 households and 26,194 individuals, provides an overview of single-ingredient acetaminophen (Tylenol®) use among a sample of nationally representative American households, Table 10-1. Based on this data, the average number of single-ingredient acetaminophen (Tylenol®) dosage units (325mg, 500mg and 650mg products) taken per day ranged from 2.5 to 3.7. Commonly treated conditions included joint pain/stiffness, back pain, acute pain, headache,

neck/shoulder pain, and muscle aches and pains. For the 325-mg tablet strength and 650-mg extended-release tablet strength, joint pain/stiffness was the most common condition treated at 40% and 73%, respectively. For the 500-mg tablet strength, headache (simple, severe, sinus and migraine) was the most common condition at 46%.

Table 10-1. 2008 TNS[a,b] Ailment Diary Data For Various Dosing Strengths of McNeil Single-Ingredient Adult OTC Products

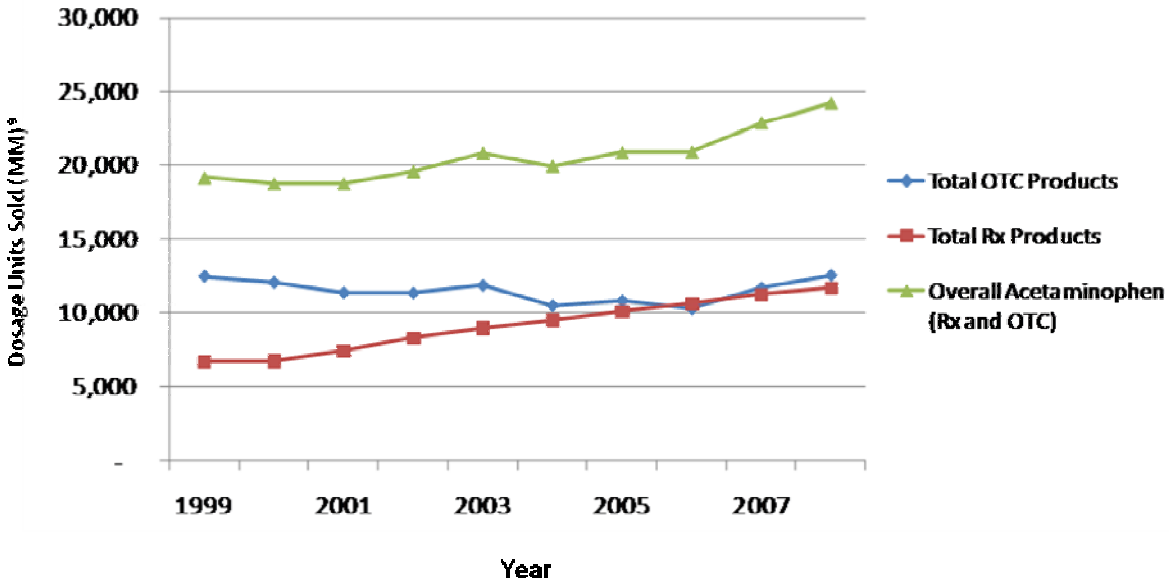
	325 mg Tylenol® Products (317 respondents)	500 mg Tylenol® Products[c] (2165 respondents)	650 mg Tylenol® Products[d] (486 respondents)
Average age of user in years	48.4	47.0	56.1
Gender of users, males/females (%)	25/75	31/69	31/69
Number of treatment occasions per year	1,672	18,201	9,171
Most commonly treated conditions (% of total number of treatment occasions)			
Back Pain	18%	25%	22%
Headaches (includes simples, severe, sinus and migraine)	27%	46%	<10%
Muscle aches/pains	<10%	20%	11%
Joint pain/stiffness	40%	19%	73%
Neck/shoulder pain	14%	16%	18%
Pain in hands/fingers	<10%	<10%	11%
Acute pain	11%	12%	20%
Joint pain/stiffness (non-arthritis)	<10%	12%	12%
Average number of conditions treated per treatment occasion	1.7	2.3	2.2
Average number of dosage units[e] taken per day	2.5 (810 mg/day)	3.1 (1550 mg/day)	3.7 (2405 mg/day)
Average number of days used over a 4-week period	2.9	4.0	8.0

a: TNS is global market research company
b: 2008 data includes 11,473 households and 26,194 individuals
c: Includes Tylenol® 500 mg Rapid Release Gels and 500 mg Extra Strength Tylenol® formulations
d: Includes Tylenol® Arthritis Pain and Tylenol® 8 Hour
e: Dosage unit is defined as a single tablet, caplet, or gel cap

10.2.2 Recent Marketplace Trends in Consumer Use of Analgesic Products

Based on IMS Health, MIDAS data, acetaminophen-containing products (OTC and prescription) are among the most frequently used medicines throughout the US [2]. As shown in Figure 10-1, acetaminophen-containing products in the US had a compound annual growth rate (CAGR) of 2.6% over the period of 1999 to 2008. The OTC market (volume) was fairly stable with a CAGR of 0.1%. In contrast, the prescription acetaminophen-combination products showed a clear increase during the same period with a CAGR of 6.4%.

Figure 10-1 OTC and Prescription Acetaminophen Dosage Units Sold in the US by Year (1999-2008)*



***IMS Health: MIDAS 1999 -2008; Dosage Units: 1 dosage unit= 1 pill = 5 ml**

The Slone Survey™, which has surveyed medication use in the US on an ongoing basis since 1998, provides the most currently available nationally representative information on medication use. The Slone Survey shows 19-23% of adults report taking acetaminophen-containing products in the preceding week [3,4,5,6]. In 2005, the one-week prevalence of adult use was 20% for acetaminophen, 17% for aspirin, 16% for ibuprofen, and 4.3% for naproxen and in 2006 the corresponding percentages were 19%, 18%, 17%, and 4.7%,

respectively. Based on the 2005 US population, there are an estimated 45 million adult users of acetaminophen (OYC and prescription) products in any given week.

10.2.3 Consumer Usage Patterns of Acetaminophen

Recently available information shows that the overwhelming majority of consumers report taking acetaminophen at the labeled OTC doses. However, as with any product, acetaminophen products can be misused either intentionally or inadvertently.

10.2.3.1 Slone Survey

In order to better understand utilization patterns of OTC acetaminophen-containing products and prescription acetaminophen-combination products, McNeil requested that the Slone Epidemiology Center conduct supplemental analyses of data from the Slone Survey. These supplemental analyses were conducted using data collected from February 1998 to August 2001 and from January 2004 to April 2007 [7,8,9].

Table 10-2 provides a summary of the 1998-2001 and 2004-2007 survey data and addresses type of product exposure, dose exposure, and number of acetaminophen products used. While the 1998-2001 data was reported as a three-year total, the 2004 through 2007 data was reported as annual totals. For purposes of comparison in this report, an average for the entire 2004-2007 period was calculated. The Slone Survey findings show that of consumers who report using acetaminophen-containing products, the vast majority report using one acetaminophen product at a time. The data also show a decline in the use of multiple acetaminophen-containing products at a time.

Table 10-2. Slone Survey – Analyses of Data Collected 1998-2001 and 2004-2007 Regarding Use of Acetaminophen in the 7 days Prior to Interview

	1998-2001 (n=6279)	2004-2007 (n=8947)
Number of acetaminophen-containing products taken		
None	78%	81%
One	20%	17%
Two	2.2%	1.6%
Three	0.2%	0.2%
Prescription status of product taken		
OTC only	19%	15%
Rx[a] only	2.2%	2.7%
Both OTC and Rx[a]	0.7%	0.5%
Prevalence of Use of Product Type		
Monopreparation only	12%	9.6%
Monopreparation plus OTC combination product	1.0%	0.8%
Monopreparation plus Rx combination product	0.4%	0.3%
OTC combination product only	6.5%	5.0%
OTC combination plus Rx combination products	0.3%	0.2%
Rx[a] combinations products only	2.2%	2.7%
Monopreparation plus OTC combination products plus Rx[a] combination products	<0.1%	<0.1%
Prevalence of Average Daily Acetaminophen Dose in the Preceding Week		
≤ 2000 mg	15%	13%
2001 - 4000 mg	1.0%	0.7%
> 4000 mg	0.2%	<0.1%
Unknown	5.4%	4.9%
None	78%	81%

[a] Prescription (Rx) acetaminophen-containing products

The 1998-2001 and 2004-2007 Slone Survey data demonstrate that virtually all individuals surveyed reported taking less than the maximum labeled dose of 4000 mg/day; there were 10 reports of an average dose of >4000 mg/day in the 1998-2001 survey and five reports in the 2004-2007 survey. In the 1998-2001 survey, among the 10 reports of an average daily

dose of > 4000 mg/day there was one report with an OTC acetaminophen single ingredient product, three reports with prescription products only, five reports with a combination of acetaminophen single-ingredient and multiple-ingredient OTC products, and one report with a combination of an acetaminophen single-ingredient OTC product and a prescription product. From 2004 to 2007, among patients using < 2000 mg/day of acetaminophen the median number of days taken in the previous weeks was two and the median total duration of use was less than one week. Use during the previous week and the total duration of use was greater in subjects who used a dose of 2001 to 4000 mg/day than in those who used < 2000 mg/day.

The 2004-2007 data analysis included an examination of the demographic characteristics of acetaminophen users and nonusers, Table 10-3. This analysis revealed a relatively higher proportion of female users (67%) compared with nonusers (55%) and there was a somewhat higher proportion of users from the South (39% users versus 34% nonusers). Users and nonusers of acetaminophen were similar with regards to age, race/ethnicity, income, and education.

A multivariate analysis of the 2004-2007 data for predictors of multiple product use did not identify any personal characteristics related to taking multiple products. There was an association between taking multiple products and the year 2005; this is consistent with the marginally higher proportion of multiple product use in that year of the survey. These findings suggest that there is no particular subgroup of patients who are at risk for use of multiple acetaminophen-containing products.

Table 10-3. Slone Survey 2004-2007 - Demographic Characteristics According to Use of Acetaminophen in the Preceding Week Among 8947 US Adults

	Users (n=1666) %*	Nonusers (n=7281) %*
Age in years		
< 40	33	30
40-49	23	20
50-59	18	21
60-69	12	14
70-79	8.2	9.3
≥ 80	5.8	6.1
Sex		
Male	33	45
Female	67	55
Race/ethnicity		
White	76	75
Black	8.3	8.0
Hispanic	8.1	8.4
Other	7.7	9.0
Region		
Northeast	19	20
Midwest	24	25
South	39	34
West	18	20
Income		
< $10,000	4.5	4.2
$10,000-19,000	11	9.2
$20,000-34,000	18	16
$35,000-64,000	25	25
$65,000-99,000	19	17
≥ $100,000	12	16
Unknown/refused	11	12
Education		
< 8 years	2.0	2.3
8-11 years	7.7	6.4
High school graduate	31	29
Some college/technical school	27	25
College graduate	17	20
Graduate school	13	15
Unknown/refused	2.6	2.2
Household size = 1	29†	30 †

*Weighted by household size.
†Unweighted

10.3 Physician Recommendations for OTC Analgesics

The National Disease and Therapeutic Index (NDTI) is an ongoing audit of US office-based physicians. The NDTI panel of physicians report on all patient contacts for two consecutive workdays each calendar quarter. The physician sample includes 28 specialty groups, projected to a universe of 488,001 physicians. Based on data from the 2006-2009 NDTI panel of physicians, acetaminophen is the OTC analgesic most commonly recommended by physicians, Figure 10-2. Physicians recommend acetaminophen more commonly than ibuprofen and aspirin for numerous conditions, including cold and flu, non rheumatoid arthritis, traumatic injuries, post-surgical pain, and headachesFigure 10-3 [10].

Figure 10-2. NDTI Physician Recommendations for OTC Analgesics in Adults (12 - month average: 2006-2009)

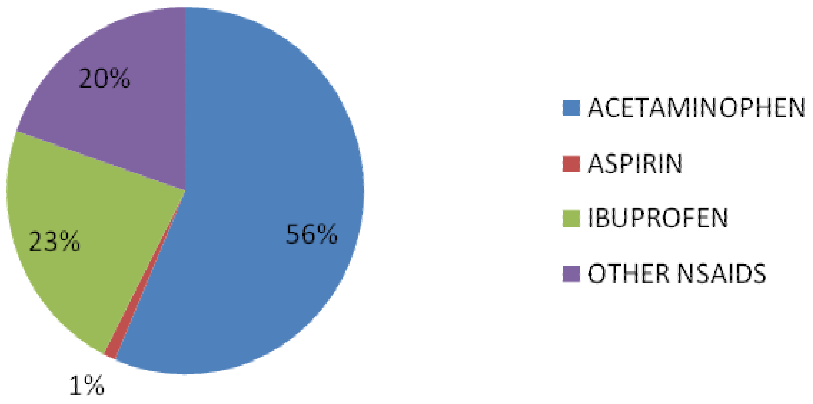
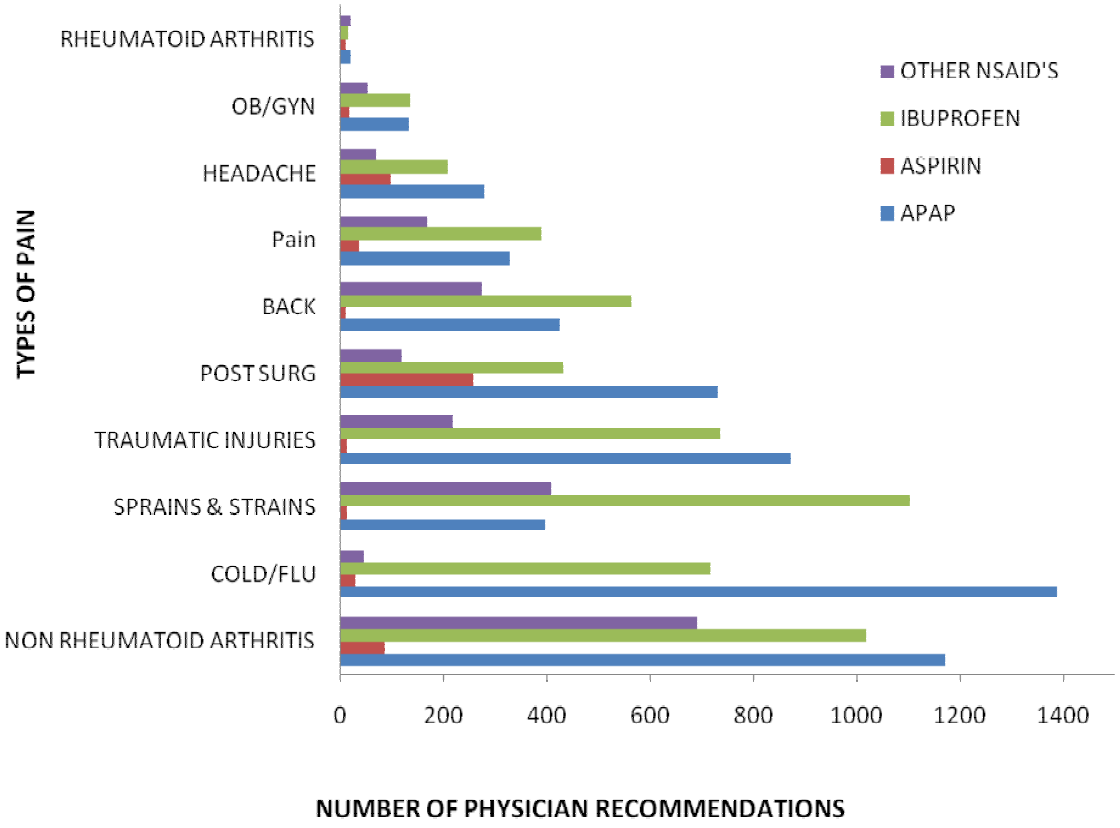


Figure 10-3. NDTI Physician Recommendations for Adult OTC Analgesics by Diagnosis (12-month average: 2006-2009)



10.4 Acetaminophen Use

10.4.1 Osteoarthritis

OA is the most common form of arthritis in the US. In 1997, 43.9 million of the estimated 959 million ambulatory care visits in the US were for a primary diagnosis of arthritis or other rheumatic condition [11]. Among these visits, 36.5 million (3.8% of all visits) were arthritis visits, the largest diagnostic category among common selected chronic conditions. It has been demonstrated that as many as 80% of a population has radiographic evidence of OA by the age of 65 years [12].

As populations age, the prevalence of OA can be expected to increase. The prevalence of self-reported, doctor diagnosed arthritis in the US has been projected to increase from 47.8 million in 2005 to nearly 67 million in 2030 [13]. By 2030, an estimated 25 million people,

9.3% of the US adult population, are expected to report activity limitations due to arthritis. While more than 50% of the expected cases of arthritis in 2030 will be in adults 65 years and older, almost one-third of cases will be in working-age adults, 45 to 64 years.

OA pain is the most common type of pain for which OTC analgesics are used [14] and acetaminophen is the most commonly used first-line treatment for OA [15,16]. Many patients with arthritis are not aware of the adverse effects associated with NSAID treatment [17]. As the population ages and the prevalence of OA increases, the proportion of the population at risk for adverse effects of NSAID treatment will continue to rise.

10.4.2 Professional Associations Recommending Use of Acetaminophen

Numerous professional associations recommend acetaminophen at doses of up to 4000 mg per day, to treat pain in the general population, as well as in patients who may be at an increased risk for NSAID-associated adverse events, Table 10-4. Many of these associations note that the safety profile of acetaminophen is more favorable than that of NSAIDs.

Table 10-4 Professional Associations Recommending OTC Acetaminophen

Association	Recommendation
Adults – Recommendations for dose of up to 4000 mg/day	
American College of Rheumatology*[18]	First-line pharmacologic therapy in patients with symptomatic OA of the knee or hip
American Society of Anesthesiologists*[19]	Around-the-clock administration of acetaminophen, NSAIDS, or COX-2 inhibitors as part of multimodal pain management
Agency for Healthcare Research and Quality**[20]	First choice in drug therapy for the treatment of mild pain associated with OA
Adults – Recommendations for treatment of pain symptoms	
Osteoarthritis Research Society International (OARSI)*[21]	Initial treatment of mild-to-moderate pain in knee or hip OA based on its safety and efficacy
European League Against Rheumatism (EULAR)***[22, 23]	First choice oral analgesic and if successful, the preferred long-term oral analgesic because of its safety and efficacy
American Pain Society**[24]	First-line analgesic for low back pain because of low cost and favorable safety profile compared with NSAIDs
American College of Physicians**[24]	
National Headache Foundation [25]	Use of simple OTC analgesics, including acetaminophen, as first line treatment for episodic tension-type headache
World Health Organization (Cancer Pain Ladder) [26]	Use of nonopioids, including acetaminophen, for mild pain
Institute for Clinical Systems Improvement [27,28]	Drug of choice for home use for general discomfort, headache, and fever reduction and initial treatment of mild to moderate somatic pain
American Pharmacist Association [29]	Recognizes that acetaminophen is a widely used first-line analgesic in the management of mild to moderate pain and may be safer than NSAIDs in elderly
Association of Women's Health, Obstetric and Neonatal Nurses*[30]	Acetaminophen demonstrates the most favorable evidence rating for OTC pharmacological intervention of cyclic perimenstrual pain and discomfort
Adults – Recommendations for special populations	
American Heart Association* [31,32,33]	Use of antipyretics, such as acetaminophen, may improve stroke prognosis Analgesic of choice in individuals who use aspirin for cardioprotection as it does not influence platelet aggregation or interfere with antithrombotic effects of aspirin First-line pharmacological management of musculoskeletal symptoms in patients with CVD, ischemic heart disease risk factors, or risk of gastrointestinal bleeding

Association	Recommendation
Adults – Recommendations for special populations	
American College of Gastroenterology**[34]	Use in general population, as well as for patients with ulcers and individuals with chronic pain from arthritis and other causes
National Heart, Lung and Blood Institute [35]	Use in aspirin-sensitive patients to avoid acute bronchoconstriction
American Geriatrics Society**[36]	Drug of choice for mild to moderate musculoskeletal pain in older persons
National Kidney Foundation [37]	Non-narcotic analgesic of choice for episodic use in patient with underlying renal disease
American Association for the Study of Liver Disease [38]	Recommends during the initial treatment of hepatitis C to ameliorate side effects of (peg)interferon alfa and ribavirin
National Digestive Diseases Information Clearinghouse [39]	Acetaminophen or NSAID may be helpful for muscle aches and low-grade fever when using alpha interferon and peginterferon in patients with chronic hepatitis C
Pediatrics	
	Use in neonates in the later postoperative period after minor procedures or as adjunct to other measures
American Academy of Pediatrics**** [40, 41, 42]	States that acetaminophen 15mg/kg per dose every 4 hours is used for fever
	Recommends the use of acetaminophen as safest analgesic for use in lactating women
Advisory Committee on Immunization Practices (ACIP) of the CDC*** [43]	Use to alleviate the discomfort and pain of pediatric vaccination, along with nonpharmacologic comfort measures
American Academy of Family Physicians [44]	Recommends the use of acetaminophen for treatment of acute otitis media pain

CVD = cardiovascular disease, NSAID = nonsteroidal anti-inflammatory drug, OA = osteoarthritis, OTC = over-the-counter, COX-2 – Cyclo-oxygenase 2 inhibitors
* Literature review and peer review process;
** Literature review and critical review process to get clinician feedback;
*** Professional judgment of healthcare professional;
**** Peer review of other organization's guidelines

10.5 Conclusions

Many patients relieve pain and fever with use of OTC acetaminophen; data shows that this use is mostly consistent with the labeling and/or with the recommendations of many professional associations. Some professional associations note that acetaminophen is the preferred analgesic for use in subpopulations at increased risk for NSAID-related adverse effects, such as the elderly, patients with renal disease, and patients with ulcer disease.

If acetaminophen availability were limited, patients would seek alternative treatments for pain and fever. While NSAIDs may provide an alternative choice in some patients, use of NSAIDs would not be recommended due to safety concerns in certain subpopulations. However, since many patients have limited knowledge regarding safety concerns with NSAIDs [14], it is likely that some patients at risk for NSAID-associated complications would use these products inappropriately if acetaminophen availability was limited. Consequently, there might be an increase in medication-related medical problems.

10.6 Reference List

1. TNS – The Sixth Sense of Business™. Ailment Diary: Adult Pain Domain. TNS – The Sixth Sense of Business™, London, UK, September 2008. (Data on file)
2. IMS Health: MIDAS 1999-2008.
3. Kaufman DW, Kelly JP, Rosenberg L et al. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone Survey. JAMA 2002;287:337-344.
4. Slone Epidemiology Center. Patterns of medication use in the United States. Results of a population-based telephone survey. 2004. Available at: http://www.bu.edu/slone/SloneSurvey/SloneSurvey.htm. Accessed June 1, 2009
5. Slone Epidemiology Center. Patterns of medication use in the United States. Results of a population-based telephone survey. 2005. Available at : www.bu.edu/slone/SloneSurvey/SloneSurvey.htm. Accessed June 1, 2009.
6. Slone Epidemiology Center. Patterns of medication use in the United States 2006. A report from the Slone Survey. Available at http://www.bu.edu/slone/SloneSurvey/AnnualRpt/SloneSurveyWebReport2006.pdf Accessed June 1, 2009.
7. Slone Epidemiology Center. Analgesic use in the adult population of the United States: acetaminophen, aspirin, ibuprofen, and naproxen. Results of a population-based telephone survey, 1998-2001. McNeil Consumer Healthcare data on file, October 2001.
8. Slone Epidemiology Center. Analgesic use in the adult population of the United State in 2004-2005: acetaminophen, aspirin, ibuprofen, and naproxen. Results of a population-based telephone survey. McNeil Consumer Healthcare data on file, December 2006.
9. Slone Epidemiology Center. Acetaminophen use in the adult population of the United State in 2004-2007. Results of a population-based telephone survey. McNeil Consumer Healthcare data on file, May 2009.
10. IMS Heath, National Disease and Therapeutic Index (NDTI), 2009
11. Hootman JR, Helmick CG, Schappert SM. Magnitude and characteristics of arthritis and other rheumatic conditions on ambulatory medical care visits, United States, 1997. Arthritis Rheum 2002;47:671-681.
12. Kellgren JH, Lawrence JS. Osteo-arthritis and disk degeneration in an urban population. Ann Rheum Dis 1958;17:388-397.
13. Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. Arthritis Rheum 2006;54:226-229.
14. Wilcox CM, Cryer B, Triadafilooulos G. Patterns of use and public perception of over-the-counter pain relievers: Focus on Nonsteroidal Antiinflammatory drugs. J Rheumatol 2005;32:2218-2224.
15. Jawad AS. Analgesics and osteoarthritis: are treatment guidelines reflected in clinical practice? Am J Ther 2005;12:98-103.
16. Porcheret M, Jordan K, Jinks C, et al. Primary care treatment of knee pain—a survey in older adults. Rheumatology 2007;46:1694-1700.

17. Ornbjerg LM, Andersen HB, Kryger P, et al. What do patients in rheumatologic care know about the risk of NSAIDs? J Clin Rheumatol 2008;14:69-73.

18. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905-1915.

19. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting. Anesthesiology 2004;100:1573-1581.

20. Agency for Healthcare Research and Quality. Choosing Non-Opioid Analgesics for Osteoarthritis. March 2009; AHRQ Publication No. 06(07)-EC009-3.; available at: http://effectivehealthcare.ahrq.gov/repFiles/Osteoarthritis_Clinician_Guide.pdf. Accessed: May 7, 2009.

21. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137-162.

22. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007;66:377-388.

23. Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005;64:669-681.

24. Chou R, Qaseem A, Snow V, et al, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians and the American College of Physicians/American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med. 2007;147:478-491.

25. Ruoff G, Urban G. Treatment of primary headache: episodic tension-type headache. In: Standards of care for headache diagnosis and treatment. Chicago: National Headache Foundation; 2004:53-58.

26. World Health Organization. WHO's Pain Ladder. Available at: http://www.who.int/cancer/palliative/painladder/en/. Accessed: May 7, 2009.

27. Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of respiratory illness in children and adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Jan. Available at: http://www.icsi.org/respiratory_illness_in_children_and_adults_guideline_/respiratory_illness_in_children_and_adults_guideline_13116.html. Accessed May 12, 2009.

28. Institute for Clinical Systems Improvement (ICSI). Assessment and management of acute pain. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Mar. Available at: http://www.icsi.org/pain_acute/pain_acute_assessment_and_management_of_3.html. Accessed May 21, 2009.

29. American Pharmacist Association. A Pharmacist's Guide to the Clinical Assessment and Management of Pain 2004. Available at:

http://www.pharmacist.com/AM/Template.cfm?Section=Search1&section=Pain_Management_Files&template=/CM/ContentDisplay.cfm&ContentFileID=2041. Accessed: May 7, 2009.

30. Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). Cyclic perimenstrual pain and discomfort: nursing management. Evidence-based clinical practice guideline. Washington (DC): Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN); 2003. Available at: http://www.guideline.gov/summary.aspx?dpc_id=7199&nbr=004302&string=perimenstrual. Accessed May 15, 2009.
31. Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke. Stroke 2007;38:1655-1711.
32. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxgenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809-1817
33. Antman EM, Bennett JS, Daugherty A, et al. AHA scientific statement: use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007 Feb 26 [published online]; 115
34. American College of Gastroenterology (ACG). Safe & Appropriate Options for Pain Management and the Prevention of NSAID-Induced GI Injury & Bleeding: A Reference for Primary Care Physicians. Available at: http://www.gi.org/patients/pdfs/ACGUlcerPhysRefGuide.pdfAccessed: May 7, 2009.
35. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program 2007. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed May 7, 2009.
36. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. The Pharmacological Management of Persistent Pain in Older Persons (2009) Guideline Recommendations. Available at: www.americangeriatrics.org/education/pharm_management.shtml. Accessed: May 7, 2009.
37. Henrich WL, Agodoa LE, Barrett B, et al. Analgesics and the kidney: summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an Ad Hoc Committee of the National Kidney Foundation. Am J Kidney Dis 1996; 27:162-165.
38. FR Doc E9-9684. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/E9-9684.htm. Accessed: May 7, 2009.
39. National Digestive Diseases Information Clearinghouse. http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/index.htm Accessed May 7, 2009.

40 American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776-789.

41 American Academy of Pediatrics Committee on Drugs. Prevention and management of pain in the neonate: an update. Pediatrics 2006;118:2231-2241.

42 Baraff LJ, Schriger JW, Bass GR, et al. Practice Guidelines for the Management of Infants and Children 0 to 36 Months of age with fever without source. Pediatrics 1993;92;1-12.

43 Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP). Diptheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Morb Mortal Wkly Rep 1991;40:1-28

44 American Academy of Family Physicians. Diagnosis and management of acute otitis media. Available at: http://www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/clin_recs/otitismedia.Par.0001.File.dat/final_aom.pdf Accessed May 7, 2009

SECTION 11 PACKAGE SIZE AND PACKAGE CONFIGURATION RESTRICTIONS

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11 PACKAGE SIZE AND PACKAGE CONFIGURATION RESTRICTIONS

11.1 FDA's Areas of Concern

FDA has proposed establishing package size limits for OTC medicines as Option 2 in the document titled, Acetaminophen Overdose and Liver Injury – Background and Options for Reducing Injury, included in FDA's May 22, 2009 background package for the June 29-30, 2009 joint advisory committee meeting. FDA states that the intended effect of package size restrictions is "to decrease the incidence of intentional ingestion of large overdoses by making it more difficult to accumulate large numbers of tablets". In addition, FDA states that "blister packs could also help consumers track how many pills they have taken".

11.2 Key Points

- Given the conflicting outcome data in the UK and limitations of the available reports, the evidence for public health benefit from OTC acetaminophen package size or package configuration restrictions is not convincing.
- Data in countries other than the UK generally do not support a positive impact of package size restrictions.
- While package sizes and configurations vary worldwide, within a country there are similar package sizes and configurations for all OTC analgesics.
- The frequency of self-poisoning as a method of suicide is lower in the US compared with the UK.
- If package size restrictions were mandated for selected OTC analgesics, eg, only required for acetaminophen, the potential for and the consequences of patients and consumers switching to other OTC drugs should be considered.
    - Available data suggest that switching from use of acetaminophen to NSAIDs may result in more people dying from NSAID-associated gastrointestinal bleeding and renal failure than those potentially spared from acetaminophen-associated liver injury.

11.3 Introduction

Package size and package configuration (eg, blister packages) restrictions for over-the-counter (OTC) acetaminophen medicines have been implemented in countries such as the UK and Ireland in an effort to reduce acute acetaminophen overdose in adults, particularly those associated with suicides or suicide gestures. Available data from these countries evaluating the effect of limitations on package size and configuration are summarized in the following sections.

11.4 Summary of Package Size Restrictions Worldwide for OTC Analgesics

Table 11-1 and Table 11-2 provide summaries of the availability of OTC analgesics worldwide. These data indicate that while package sizes and configurations vary worldwide, within a country there are similar package sizes and configurations for all OTC analgesics. In many countries outside of the United States, OTC analgesic package sizes are determined by health authorities at the time of product approval and are based on the labeled maximum daily dose and labeled duration of use (Table 11-2). In addition, outside of the United States, OTC analgesics are typically sold in blister packs. Thus, package sizes outside of the United States are generally smaller than those available in the United States. In five countries (Denmark, Germany, Ireland, United Kingdom, and Sweden), further restrictions have been made for safety reasons (Table 11-1).

Table 11-1. Summary of Package Sizes Worldwide for OTC Analgesics - Countries with Specific Regulations Concerning Package Size Restrictions

	Maximum Strength/Maximum Number per Pack							
	Paracetamol		Ibuprofen		Aspirin		Naproxen	
Country	mg	Number	mg	Number	mg	Number	mg	Number
Denmark –GSL	500 mg	20 tabs	200 mg	30 tabs	500 mg	10 tabs	Rx	
Germany	500 mg	20 tabs (10 g) Apr 1, 2009	400 mg	50 tabs No Restr	500 mg	1000 tabs No Restr	250 mg/dose	30 tabs
Ireland - Pharmacy	500 mg 600 mg 1000 mg 250 mg/5 mL 120 mg/5 mL	24 20 12 140 mL	200 mg	No Restrictions	500 mg 300 mg	24 tabs 50 tabs	POM	
Ireland - GSL	500 mg 600 mg 1000 mg 250 mg/5 mL 120 mg/5 mL	12 10 6 60 mL 60 mL	Not Available GSL	Not Available GSL	500 mg 300 mg	16 24	POM	
UK - Pharmacy	500 mg	32 tabs	400 mg 600 mg CR	50 g	500 mg 75 mg	32 100 tabs	250 mg (500mg/dose; 750mg/day)	9 tablets 1 indication - dysmenorrhea (ages: 15-50 only)

Table 11-1. Summary of Package Sizes Worldwide for OTC Analgesics - Countries with Specific Regulations Concerning Package Size Restrictions

	Maximum Strength/Maximum Number per Pack							
	Paracetamol		Ibuprofen		Aspirin		Naproxen	
Country	mg	Number	mg	Number	mg	Number	mg	Number
UK – GSL	500 mg	16 tabs	400 mg (Adult) 200 mg (Pediatric)	16 tabs 20 (doses)	500 mg 325 mg (effervescent)	20 tabs 30 tabs (effervescent)	--	--
Sweden	500 mg	20	400 mg	30 tabs	500 mg	60	250 mg	20 tabs

Abbreviations: CR=controlled release, GSL=general sales list, POM=prescription only medicine.

Table 11-2. Summary of Package Sizes Worldwide for OTC Analgesics - Countries with No Specific Regulations Concerning Package Size Restrictions – Pack Size Determined by Health Authorities at Time of Approval

	Maximum Strength/Maximum Number per Pack							
	Paracetamol		Ibuprofen		Aspirin		Naproxen	
Country	mg	Number	mg	Number	mg	Number	mg	Number
Austria*	650 mg	30 tabs	400 mg 1200 mg/day	No Restr	1000 mg 3g/day	No Restr	200 mg 600 mg/day	No Restr
Belgium*	500 mg	20 tabs	400 mg 2500 mg/day	30 tabs	500 mg 4g/day	100 tabs	220 mg 1250 mg/day	30 tabs
Finland*	500 mg (oral powder, tablet) 250 mg (oral solution, suppository)	12 x 500 mg tabs 6 g (oral powder, tablet) 6 x 250 mg suppository 1,5 g (suppository)	400 mg	30 x 400 mg tabs 12 g	500 mg No Restr	No Restr	Rx	
France*	500 mg (max 1000mg/unit)	8 tabs 8g/pack	400 mg	6g/5days per pack	1000 mg 3g/day	30 tabs	220 mg/tab	3330 mg/pack
Greece*	500 mg	24 tabs	200 mg	60 tabs	500 mg	24 tabs	Rx	

Table 11-2. Summary of Package Sizes Worldwide for OTC Analgesics - Countries with No Specific Regulations Concerning Package Size Restrictions – Pack Size Determined by Health Authorities at Time of Approval

	Maximum Strength/Maximum Number per Pack							
	Paracetamol		Ibuprofen		Aspirin		Naproxen	
Country	mg	Number	mg	Number	mg	Number	mg	Number
Italy*	500 mg 4 g/day	30 15 g/5 day OTC but no advertising allowed Full OTC: 20 tabs, 500 mg	400 mg 1200 mg/day	12 tabs	500 mg 6g/day	20 tabs	220 mg/660 mg x day	26
Netherlands*	500 mg (GSL)	20 tabs	400 mg (Pharmacy and Drugstore)	20 tabs	500 mg (Pharmacy and Drugstore)	10, 12, 20, 24 tabs	220 mg 275 mg 550 mg (Pharmacy and Drugstore)	3, 10, 20, 30, 40 tabs 20 tabs 10 tabs
Spain*	650 mg 1000 mg	10-20 tabs / pack 12 sachets	400 mg	10-20 tabs / pack	500 mg	10-20 tabs / pack	Rx 200 mg	Rx 10-20 tabs / pack
Portugal*	500 mg	24	200 mg	24 – 60	500 mg	20	200	24

* Pack size determined by health authorities at time of product approval, dependent on maximum daily dose and labeled duration of use; OTC medicines (oral solids) are typically sold in blisters
Abbreviations: GSL=general sales list.

11.5 Review of Published Literature on Effect of Package Size Restrictions

Package size restrictions for OTC analgesic medicines have been implemented in countries such as the UK (for acetaminophen and aspirin) and Ireland (for acetaminophen) in an effort to reduce acute analgesic overdose in adults, particularly those associated with suicides or suicide gestures.

On September 16, 1998, the UK introduced legislation that limited the number of OTC tablets of acetaminophen and aspirin to a maximum of 32 per sale (16 g) when purchased through a pharmacy (although up to 100 tablets were allowed at the discretion of the pharmacist) and 16 per sale (8 g) when purchased through other retail outlets. In non-pharmacy outlets, acetaminophen had previously been available in packages of 25 tablets. In addition, overdose warnings were required on packets and leaflets in packets. Other changes included a voluntary code to sell no more than two packages of 16 tablets in a single transaction. While not required by legislation, acetaminophen is almost exclusively sold in blister packs in the UK; this occurred around the same time as the legislation, making it difficult to separate the potential effects of these changes. The rationale for package size restriction was based on the finding that acute intentional overdose in adults (suicide attempts or suicide gestures) had been perceived as a major health problem in the UK [1,2,3,4]. As many cases of acute intentional overdose were impulsive [5] and availability appeared to be a factor in choice of self-poisoning agent [6], it was theorized that limiting package size would reduce the number of acute intentional overdoses.

11.5.1 Search Criteria

A comprehensive worldwide literature search was performed using two online bibliographic databases, MEDLINE® from 1950 through April 30, 2009 and EMBASE® from 1988 through April 30, 2009. Index terms or descriptors and text terms and text phrases included acetaminophen, paracetamol, government regulation, drug packaging, legislation, drug, drug legislation, overdose, poisoning, toxicity, intoxication, fatality, mortality, or suicide. The final combination of terms was limited to reports of humans. Each citation's bibliographic record and abstract were reviewed. If the bibliographic record did not provide sufficiently detailed information, the full publication was reviewed. In addition, some relevant studies were identified based on the reference lists of selected articles. Table 11-3 contains summaries of published studies of the effect of acetaminophen package size restrictions.

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Prince 2000 [9] England UK[a]	10/95-12/99	• Admissions to the Freeman Liver Unit (Newcastle-upon-Tyne), number with APAP hepatotoxicity, severity • National liver transplantation requests due to APAP toxicity from the UK Transplant Special Support Authority (UKTSSA)	• Median monthly number of referrals to liver unit ↓'d from 2.5 to 1 after restrictions (p<0.02). • Nationally, median monthly number of referrals for transplants ↓'d from 3.5 to 2 after restrictions (p<0.02). • Overdose severity (of cases referred to the liver unit) remained constant throughout the study
Turvill 2000 [11] England UK[a]	9/95-8/99	• Royal Free Hospital in London, England, all APAP overdoses and benzodiazepine overdoses	• 21% ↓ in APAP overdoses and a 64% ↓ in severe APAP overdoses (N-acetylcysteine or methionine therapy was indicated to prevent acute liver injury) in year following APAP restrictions. Benzodiazepine overdoses remained stable.
Hawton England and Wales 2001 [13] and 2002 [7] UK[a]	9/96-9/99	• England and Wales mortality data for those ≥12 years where only APAP or salicylates were involved • 5 liver units in England, admissions after APAP overdose, patients listed for liver transplantation, and patients receiving liver transplants • 7 hospitals, self-poisonings with APAP and salicylate products • IMS monthly sales data	• After restrictions, 21% ↓ in number of deaths due to APAP alone (p=0.01). • For APAP poisonings, number of patients admitted to liver units ↓'d by 30%, number who received liver transplantation ↓'d by 66%. • Proportion of non-fatal overdose cases involving APAP did not change, but absolute number ↓'d (p<0.001) by 11%. Proportion involving APAP combination products ↑'d (p=0.001) and involving APAP alone ↓'d (p=0.001). Proportion involving > 32 tablets ↓'d by 17% (p=0.01). • Sig ↓ in the mean number of APAP tablets sold per pack, a sig ↑ in number of packs sold, and no sig change in total number of tablets sold. • No sig change in highest APAP blood concentration.
Thomas 2001 [14] Wales UK[a]	2/98-8/98 and 2/99-8/99	• Admissions at Withybush General Hospital in Pembrokeshire, overdose	• 116 admissions for overdose in 1998 and 112 in 1999 • 52 (45%) of overdoses were APAP poisonings in 1998 and 40 (36%) in 1999 • 68% of patients took > 16 APAP tablets in 1998, versus 51% in 1999 • Non-APAP poisonings ↑'d from 64 cases in 1998 to 72 cases in 1999 • Average time spent in hospital was the same during both periods (2.6 days)
Hawton 2003 [20] England UK[a]	1990 – 2000	• Oxford Monitoring System for Attempted Suicide, adolescents presenting with deliberate self-harm to a general hospital, overdose	• 1583 subjects with 2120 episodes presented to the hospital • Frequency of APAP overdose ↑'d between 1991 and 1997,↓'d in 1998 and 1999, but ↑'d in 2000 • Antidepressant overdoses ↑'d between 1996 and 2000

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Wilkinson 2002 [21] England UK[a]	1995 - 2000	• National database, hospital admissions for deliberate self-harm, all ages	• APAP use as a main diagnosis ↓'d from 77 to 67/100,000 from 1997/98 to 1999/2000; use as a subsidiary diagnosis ↑'d by 63.3% over study period. • Sedative/hynoptic and psychotropic drug use as a main diagnosis rose from 56 to 75/100,000 from 1995/96 to 1999/2000; use as a subsidiary diagnosis increased by 37.6% over study period.
O'Loughlin 2005 [22] England UK[a]	1981 – 2000	• Parasuicide Counselling Group, patients ≥15 years old referred after ER visit for deliberate self-harm	• % of deliberate self-harm episodes in which APAP was used ↑'d over the 20-year period, from 5-10% in the early years, to a third at the start of the 1990s, to nearly 50% by the mid-1990s; % ↓'d starting in 1998 and reached 40% to 43% in 1999.
Hughes 2003 [15] England UK[a]	4/95-1/02	• University Hospitals, Birmingham, admissions for APAP overdose • Queen Elizabeth Hospital liver unit, admissions for APAP-induced hepatotoxicity	• Admissions for APAP overdose ↓'d from 360 to 250 per year after restrictions • Admissions to the liver unit with APAP-induced hepatoxicity ↓'d from 76 to 38 per year after restrictions
Langford 2003 [12] England UK[a]	1998 – 1999, 2002	• Admissions to an NHS Trust, total and APAP overdoses, admissions with APAP toxicity to a tertiary liver unit, and coroner's records for drug-related and APAP-related deaths	• 6 mos pre-legislation vs 6 mos in 1999: number of APAP hospital admissions, hospital APAP overdoses with >32 tablets, APAP admissions to the liver unit, and total hospital overdoses ↓'d ($p < 0.05$); APAP-related deaths (liver unit or coroner records) did not change sig. • In 2002, number of APAP hospital admissions, hospital APAP overdoses with >32 tablets, APAP overdoses with >32 tablets admitted to the liver unit, and total hospital overdoses still lower than before restrictions ($p < 0.05$)
Morgan 2005 [17] England and Wales UK[a]	1993-2002	• National mortality data for England and Wales, APAP related deaths • Hospital admissions, primary diagnosis of APAP poisoning	• Mortality rates with APAP only ↓'d over time and were 4.5/million in 1997, 2.8/million in 1999, 3.1/million in 2001, and 2.2/million in 2002; mortality rates with APAP combination products remained relatively constant • ↓ in APAP only mortality rates was consistent with overall trend in mortality rates and for other drug poisonings, excluding opioids and drugs of misuse • Hospital admissions due to APAP poisonings ↓'d post restrictions and were about 27,000 in 1995/1996, 33,000 in 1997/1998, and 25,000 in 2001/2002.

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Morgan 2007 [23] England and Wales UK[a]	1993 - 2004	• National mortality data for England and Wales, drug-poisoning deaths, using an interrupted time-series analysis	• Age standardized APAP mortality rate ↑'d from 8.1/million in 1993 to 8.8/million in 1997, falling to 5.3/million in 2004. Antidepressants, aspirin, and APAP combination products demonstrated a similar ↑ until 1997 followed by a ↓ after restrictions in age standardized mortality rate. The observed ↓ in APAP mortality may have been part of a wider trend in ↓'d drug-poisoning suicide, and not due to package size restrictions. • Non-drug poisoning suicide also ↓'d from 1993 – 2004
Hawton 2004 [16] England, Wales, and Scotland UK[a]	1993-2002	• England and Wales mortality data, patients ≥ 12 years for APAP, salicylates, and ibuprofen • Liver units in England and Scotland, number of patients admitted after APAP overdose, listed for liver transplantation, and undergoing liver transplantation • 5 general hospitals in England, presentations for self-poisoning with APAP, salicylates, ibuprofen, and other drugs • IMS UK sales data	• ↓ ($p<0.001$) in deaths related to APAP (-34%) and salicylates alone (-70%) in 2nd and 3rd years post restrictions; few deaths involved ibuprofen • Admissions to liver unit for APAP poisoning ↓'d from 349 before restrictions to 230 in the 4 years after, listings for liver transplantation ↓'d from 43 to 30, and transplants ↓'d from 32 to 21.5 • For non-fatal self poisonings, there was a 24% ↓ with APAP alone in the year after restriction followed by ↑'s in next 2 years (but still < before restrictions), no sig change with salicylates alone after restrictions, and an ↑ of 51% with ibuprofen alone in the 2nd and 3rd years after restrictions • Number of tablets taken in APAP alone and salicylate alone non-fatal overdoses ↓'d ($p\leq0.02$) in the 3 years after restrictions • Non-fatal overdoses of > 32 tablets of APAP alone ↓'d ($p=0.04$) in the 2nd and 3rd years after restrictions • 520 million APAP tablets sold in 1996-7 and 580 million sold in 2001-2; sales of aspirin tablets halved during study period
Morgan 2007 [19] Hawkins 2006 [18] England UK[a]	1996 – 2004	• Guy's and St. Thomas' poison center database, severity of APAP overdoses with adult formulations	• Post 1998, % of APAP overdoses taking 16 tablets ↑'d to nearly 50%; % taking 17-32 ↓'d from 36% to 30% and percent taking 33-100 tablets ↓'d from 25% to 19%, % taking >100 tablets remained constant at about 1% • From 1999 onward, median number of tablets ↓'d from 25 to 20 for males and from 20 to 16 for females

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Sheen 2002 [58] England, Wales, Northern Ireland UK[a]	1998-2000	• IMS UK sales data for APAP 500 mg, ibuprofen 200 mg and 400 mg, and aspirin 75 mg and 300 mg tablets	• Total mass of OTC APAP ↓'d from 409,054,172 g in 1998 to 198,566,850 g in 1999 and to 166,456,260 g in 2000 • Total mass of OTC aspirin ↓'d from 66,465,780 g in 1998 to 21,943,740 g in 1999 and to 15,448,710 g in 2000 • Total mass of OTC ibuprofen ↑'d from 26,453,320 g in 1998 to 29,616,100 g in 1999 and to 45,929,400 g in 2000
Robinson 2000 [10] Northern Ireland UK[a]	1/98-6/98 vs 1/99-6/99	• 5 general hospitals in the Belfast area, patients with acute APAP self-poisoning, APAP amount ingested, serum APAP concentrations, antidote administration, hospital admission, liver enzymes levels, and INR.	• No sig change in the number of patients presenting with APAP poisoning (590 to 594), the number of patients admitted to hospital, the serum aspartate aminotransferase level at 24-48 hours, or in INR • ↓ in APAP ingested (10 to 8 g, p=0.004), serum APAP concentrations at 4-6 h ↓'d from 37 to 27 mg/L (p=0.003), and antidote administration ↓'d from 183 patients to 149 patients (p=0.03)
Bateman 2003 [35] Scotland UK[a]	1990-1999	• National hospital discharge and mortality data, all poisons, APAP, opioids, and antidepressants	• Annual discharge rates for total overdoses and APAP overdose ↑'d from 1990 and 1997, and ↓'d after 1997 (after restrictions) • Overall mortality from overdoses ↓'d after 1993; there was no sig trend in overall APAP overdose mortality • Discharge rate for antidepressant overdose ↑'d 2-fold during study and did not ↓ after 1997; the discharge rate for opioid overdose ↑'d sig during study
Bathgate 2000 [27] Scotland UK[a]	11/92-3/00	• Admissions to Scottish Liver Transplant Unit, APAP poisoning	• No sig differences before and after restrictions in the mean number of monthly admissions (3.9 and 3.5), in the number of APAP tablets taken in overdose (69 and 58), or in the % of patients who died or had transplants (43% and 35%). • Mean time to presentation ↓'d (p<0.001) from 28 h to 13 h after restrictions
Laing 2001 [28] Scotland UK[a]	1996-2000	• Scottish Poison Information Bureau, telephone inquiry statistics	• APAP inquiries, as a % of total inquiries, ↓'d slightly with 9.7% in 1996/1997, 9.1% in 1997/1998, 8.8% in 1998/1999, and 8.9% in 1999/2000 • % of patients ingesting >8 g remained stable after restrictions: 1996/1997 (44%), 1997/1998 (35%), 1998/1999 (33%), 1999/2000 (31%) • % of patients ingesting >16 g ↑'d after restrictions: 1996/1997 (26%), 1997/1998 (13%), 1998/1999 (17%), 1999/2000 (16%)

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Sheen 2001 [29] Scotland UK[a]	9/95-9/00	• Biochemistry database of Ninewells Hospital, Dundee, potentially hepatotoxic APAP levels	• 6336 tests were performed of which 4454 were negative for APAP. • No sig difference was observed in the number of tests with APAP level >1.3 mmol/L: after September 1998 (range was 27 to 28) compared with before September 1998 (range was 23 to 27)
Sheen 2002 [30] Scotland UK[a]	1994-2000	• National mortality data, deaths related to APAP, and deaths due to any poisonings	• 3878 poisoning deaths (1994-2000); 16.6% involved APAP • No sig difference between 1996/1997 and 1999/2000 in number of deaths due to APAP alone (1996-27, 1997-31, 1998-20, 1999-20, 2000-31) or in all APAP-related deaths (1996-96, 1997-102, 1998-93, 1999-70, 2000-112) • Mean annual death rate from APAP alone from 1994 to 2000 was 5.4 per million, and for all APAP-related deaths was 17.9 per million
Newsome 2001 [34] Scotland UK[a]	1992-2001	• Scottish Liver Transplantation Unit, admissions	• Monthly referral rate for APAP-induced acute liver injury: before (1992-1998) vs after (1998-2001) restrictions: 3.94 vs 3.57 • Monthly referral rate for APAP-induced acute liver failure: before (1992-1998) vs after (1998-2001) restrictions: 2.03 vs 1.67
Inglis 2004 [36] Scotland UK[a]	1990-2002	• National mortality data and emergency admissions data, APAP poisonings and all poisonings	• After restrictions, deaths from APAP poisonings ↓'d by 45% in 1998 but ↑'d in each of the 3 years after to reach pre-restriction levels. • Deaths from all poisonings remained stable throughout the study period. • Following restrictions, emergency admissions for all poisonings ↓'d by 10% and APAP poisonings ↓'d by 14%, but both subsequently ↑'d again.
Gorman 2007 [37] Scotland UK[a]	1995 – 2002	• National mortality data • National acute hospital discharge data	• APAP overdose rates/100,000 ↓'d after restrictions, but then ↑'d: 1997-140.3, 1998-124.2, 1999-111.6, 2000-131.3, 2001-141.5, and 2002-137.3 • Proportion of overdoses containing APAP ↓'d after restrictions, but then ↑'d: 1997-.34, 1998-.32, 1999-.30, 2000-.34, 2001-.36, 2002-.35. • APAP overdose deaths ↓'d in 1999 but ↑'d thereafter: 1997-102, 1998-94, 1999-72, 2000-113, 2001-112, and 2002-98
Bateman 2005 [33] Scotland UK[a]	1995-2003	• Hospital death and discharge data, all overdoses and APAP overdoses • Death registration data for APAP overdoses	• % of hospital poisoning death and discharges involving APAP was not sig different during study period (1995-30%, 1997-34%, 1999-30%, 2003-37%) • Number of deaths including APAP in the overdose cocktail was 83 in 1995, 110 in 1997, 79 in 1999, and 122 in 2000 • Number of overall in-hospital overdose deaths showed no sig change over time

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Bateman 2006 [31] Scotland UK[a]	1995-2004	• National mortality data and hospital discharge data, APAP poisonings and APAP overdoses	• No sig difference pre and post restrictions in the number of APAP poisoning deaths (ratio = 1.22, post vs pre p=0.19) • Proportion of in-hospital deaths attributed to APAP ↑'d during the study (ratio = 1.347, post vs pre p=0.013); the majority of APAP-associated deaths were due to Co-Proxamol (APAP combined with dextropropoxyphene HCl) • Number of poisoning hospital discharges ↓'d, including after restrictions • % of poisoning hospital discharges involving APAP in any form ↑'d sig in all age groups except for young men, even after restrictions
Bates 2006 [32] Scotland UK[a]	11/92-4/06	• Scottish Liver Transplant Unit, admissions with a severe liver injury, APAP overdoses, mortality	• Of 806 patients admitted to the liver transplant unit, 579 had liver injury due to APAP, of which 302 had fulminant hepatic failure • 278 admissions prior to restrictions (in 71 months) and 301 admissions after restrictions (90 months to April 2006). • Mortality for APAP overdose was 24.1% before and 31.2% after restrictions.
Donohoe 2000 [44] Ireland[b]	1997-1998	• National Poison Information Center in Dublin, acute APAP overdose in patients >10 years	• No sig difference in number of APAP overdoses before and after restrictions (1044 in 1997 and 976 in 1998) • Number of cases involving more than 48 tablets ↓'d slightly (127 vs 120) but was not sig; > 50% of the cases took ≤ 24 tablets
Laffoy 2001 [43] Ireland[b]	1993-1999	• National hospital admissions and survey data from 100 non-pharmacy outlets in Dublin	• Hospital admissions for APAP overdose ↑'d by 29% between 1993 and 1999, and ↓'d only by 1.9% after restrictions (from 1997 to 1999) • All nonpharmacy outlets visited allowed the purchase of 48 tablets of APAP, indicating that outlets were not complying with the voluntary guidelines.
Donohoe 2006 [45] Ireland[b]	1999 – 2003	• National Poisons Information Center, APAP overdoses in patients >10 years	• No sig difference in APAP overdoses as % of deliberate self-poisonings (pre Oct 2001-14.09%, post Oct 2001-14.10%) • Sig ↓ in APAP overdoses pre and post Oct 2001 with 13-24 tablets (34.4% to 29.1%) and those with >24 tablets (34.0% to 32.5%).
Kisely 2003 [47] Australia[c]	1996-2001	• Western Australian Health Services Research Linked Database before and after 2 periods of recall of APAP products, hospital admissions for APAP overdoses, poisoning by other agents	• Hospital admissions rate (per 100,000 person-years at risk) following overdose was 20.56 for APAP, 0.96 for aspirin, and 2.76 for ibuprofen when APAP was available in 1996-1999 and 2001 compared to 16.90 for APAP, 0.93 for aspirin, and 2.40 for ibuprofen when APAP availability was restricted in 2000; the ↓ in APAP admissions was sig (p=0.041). • Similar results were observed when accidental poisonings and deliberate self-harm were considered separately.

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Balit 2002 [46] Australia[c]	1997-2000	• National poison information center (NSW) and a regional toxicology service (HATS) before and after 2 periods of recall of APAP products, accidental and deliberate self-poisoning with APAP, ibuprofen, and aspirin, accidental pediatric poisoning	• Number of NSW calls for deliberate self-poisoning was 14,775 (1997-1999) and 4554 during recall periods in 2000 • No sig change for APAP (1997-1999-8.6%; 2000-8.1%) or aspirin (1997-1999-1.1%; 2000-1.2%) NSW calls, but an ↑ in calls for ibuprofen (1997-1999-0.9%; 2000-1.7%; p=0.001). • During recall periods, an ↑ (p=0.001) in NSW calls for accidental pediatric poisonings with ibuprofen but no sig change in calls for APAP or aspirin • Number of presentations to HATS for deliberate self-poisoning was 765 (1997-1999) and 230 during recall periods in 2000 • No sig change in % of patients presenting to HATs for APAP (1997-1998-14.0%, 2000-15.7%) or ibuprofen (1997-1998-0.8%, 2000-0.9%); ↑ for aspirin (1997-1998-0.7%, 2000-2.2%; p=0.043)
Ott 1990 [49] Denmark[d]	1978-1987	• National mortality and hospital admissions, APAP newly available OTC vs salicylates (OTC), dextropropoxyphene (prescription only), and other opioid drugs (prescription only) and suicides • Danish Drug Market Statistics, drug sales	• After OTC availability of APAP, sales ↑'d from 1 million defined daily doses (DDD) in 1978 to 47 million in 1986; ↓ in APAP overdose hospital admissions (11.6/million DDD sold in 1979 to 5.0/million DDD sold in 1986) and deaths (0.45/million DDD sold in 1979 to 0.07/million DDD sold in 1986). • Salicylate sales ↓'d (113 to 94 million DDD), but hospitalizations and deaths ↑'d; dextropropoxyphene sales were steady, but morbidity and mortality ↑'d; other opioid sales steadily ↑'d, and morbidity and mortality fluctuated • Numbers of suicides and drug-related deaths were fairly stable during study
Prior 2004 [48] Canada[e]	4/1995 – 3/2001	• National inpatient hospitalizations, before and after lifting APAP place-of-sale restrictions, inpatient hospitalizations for APAP overdose toxicity in patients ≥12 years old • ACNielsen APAP sales data	• Where restrictions were lifted, no sig change in APAP overdose hospitalizations (pre vs post: 23.18 vs 22.33/100,000) or in hospitalizations for APAP overdose and acute liver toxicity (pre vs post: 0.49 vs 0.47/100,000). • Where restrictions were lifted, no sig differences in APAP overdose hospitalizations with death (pre vs post: 0.21 vs 0.19/100,000) or in hospitalizations for APAP overdose and acute liver toxicity with death (pre vs post: 0.13 vs 0.09/100,000). • APAP sales were stable during study

Table 11-3. Summary of Published Clinical Studies of the Effects of Acetaminophen Package Size Restrictions

Author Year Country	Study Time Period	Data Sources and End Points	Results
Gunnell 1997 [50] France and UK[f]	1974-1994	• Mortality data, England and Wales • Oxford monitoring system, attempted suicide with APAP • IMS APAP sales data • Poison Center in France, mortality and morbidity of APAP poisoning	• Correlation between APAP sales and APAP non-fatal overdoses in Oxford (1976-1993, r=0.86; 95% CI 0.54, 0.96), and France (1974-1990, r=0.99; 95% CI 0.97, 1.00) • Correlation between APAP sales and APAP related suicides in England and Wales (1983-1991, r=0.72; 95% CI 0.11, 0.94), and France (1974-1990, r=0.79; 95% CI 0.50, 0.92) • Crude case fatality rates from APAP overdose were estimated as 0.4% in England and Wales and 0.1% in France.

a: In September 1998, the UK introduced legislation limiting the number of tablets of APAP sold. Supermarket packs may contain a maximum of 16 APAP 500 mg tablets (8 g total) and pharmacy packs may contain a maximum of 32 APAP 500 mg tablets (16 g total). Up to 100 APAP tablets can be sold at the discretion of a pharmacist but a prescription is required for more than 100 tablets. Specific warnings on APAP are printed on packets and on leaflets supplied with packets.

b: The October 1997 Irish Medicine Board voluntary guidelines for the sale and supply of APAP stated that non-pharmacy outlets should only sell emergency supplies of APAP in a maximum pack size of 12 tablets and just one pack should be sold on each occasion. In October 2001 new regulations came into force that gave statutory effect to the previously voluntary guidelines.

c: Products containing APAP were recalled on two occasions in 2000 following extortion threats to 2 pharmaceutical companies; Herron from March 16, 2000 until May 21, 2000 and Smith-KlineBeecham from June 6, 2000 until August 23, 2000.

d: In Denmark, all Rx and OTC drugs are sold only in pharmacies. APAP changed from an Rx to an OTC drug on January 1, 1984.

f: At the time of this study, in the UK APAP was available in unlimited quantities from pharmacies and up to 12 g could be purchased in supermarkets; in France APAP could only be purchased in pharmacies and the contents of each pack of APAP was limited to 8 g.

e: Six provinces and territories in Canada had restrictions on APAP sales (the sale of all APAP strengths >325 mg and packages with >24 tablets of any strength could only be sold in pharmacies) that were lifted in September 1999. Three provinces had no restrictions.

Abbreviations: APAP = acetaminophen, CI = confidence interval; OTC = over-the-counter; Rx = prescription; UK = United Kingdom

11.5.2 Studies of Acetaminophen Package Size and Package Configuration Limitations in the UK Show Inconsistent Results

The effect of package size and package configuration restrictions on reducing acetaminophen overdoses in the UK has been assessed by numerous investigators, with conflicting outcomes. In 2007, Hawkins et al [8] reviewed the results of studies in the UK and concluded, "The limited number of studies to date, combined with a variety of outcome measures, make it difficult to determine with accuracy whether or not the legislation has been a success. More long-term studies are needed to fully assess the impact of the legislation."

Some studies, conducted mainly in England and Wales, suggest that the introduction of package size restrictions had a positive impact on acetaminophen poisoning deaths, admissions to liver transplant units for acetaminophen poisoning, listings for liver transplantation, liver transplantation, hospital admissions for acetaminophen overdose, acetaminophen overdose as a method of deliberate self-harm, and amount of acetaminophen taken in overdose [9,10,11,12,13,14,15,16,17,18,19,20,21,22]. The extent and duration of benefit varies considerably among the studies. Decreases in large (>32 tablets) or severe (admissions to a liver unit, patients registered for liver transplantation, or use of NAC or methionine) acetaminophen overdose have been reported immediately following the package size restriction legislation in England [9,11,12,13]. In addition, Robinson et al [10] observed a decrease in the estimated median quantity of acetaminophen ingested (from 10 grams to 8 grams), but no reduction in the number of cases of acute acetaminophen self-poisoning presenting to five hospitals in Northern Ireland when comparing the six months before and after package size restrictions were introduced. Although a decline in acetaminophen overdose was reported in one hospital in Wales [14] from February to August 1999 versus the same time period during the previous year (40 and 52 patients, respectively), the number of non-acetaminophen overdoses, consisting mainly of antidepressants, antipsychotics, and sedatives, increased from 64 to 72. Similarly, Hawton et al [16] observed a decrease in fatal acetaminophen overdose during the three-year period after restrictions in England and Wales, a decrease in nonfatal acetaminophen overdose in the first year after restrictions in England followed by *increases* in the next two years (although still less than before restrictions), and an *increase* in nonfatal ibuprofen overdose in the three years following the package restrictions. Hawton et al [20] also evaluated trends in adolescents 12 to 18 years of age in Oxford, England from 1990 to 2000 presenting to a general hospital due to deliberate self-harm. The frequency of acetaminophen overdose as a method of deliberate self-harm decreased in 1998 and 1999, but increased in 2000. In addition, antidepressant overdose continued to increase during this same period. Wilkinson et al [21] evaluated trends in deliberate self-harm for

all ages in England from 1995 through 2000 using hospital admission data. While acetaminophen use as a main diagnosis fell from 77/100,000 in 1997/98 to 67/100,000 in 1999/2000, acetaminophen use as a subsidiary diagnosis increased by 63.3% over the five-year period. Sedative/hypnotic and psychotropic drug use as both a main diagnosis and a subsidiary diagnosis increased by 26.7% and 37.6%, respectively, over the same five-year period, with the combined rate of hospital admission exceeding that for acetaminophen in 1998/99 and 1999/2000. A decrease in mortality for acetaminophen only was observed in England and Wales by Morgan et al [17]; however, the authors note that this decrease may have been attributable to random variation in mortality rates. A decrease in mortality attributable to other drug poisonings was also observed over the same time period. This observation was supported by an interrupted time-series analysis for England and Wales conducted by Morgan et al [23], which demonstrated, in addition to a decrease in fatal poisoning associated with acetaminophen only, a decrease in fatal poisoning associated with aspirin, antidepressants, as well as acetaminophen combination medicines, occurred during the period 1998 to 2004. This further supports the hypothesis that the observed decline in acetaminophen mortality may not have been due to package size restrictions, but rather was part of a wider trend in the reduction of drug-poisoning suicide. The number of acetaminophen tablets sold on an annual basis in the UK [13,16] was not reduced following the establishment of package size restrictions.

In addition, it should be noted that in 2001, Hawton et al reported on the number and percent of suicides, undetermined deaths, and deaths resulting from accidental poisoning attributed to acetaminophen for three periods, the penultimate 12 months before legislation in the UK mandated package size restrictions, the 12 months before the change, and the 12 months after the change in England and Wales [13]. Hawton et al reported the percent of deaths attributed to acetaminophen alone as 9.0%, 8.3%, and 7.0% for these three periods, respectively, suggesting that the reduction in the percent of deaths due to acetaminophen started before the legislation. Similarly in 2004, Hawton reported the number of admissions for liver transplants due to acetaminophen poisonings in six liver transplant units in England and Scotland as 369, 329, and 271 for the same three reporting periods as reported in 2001 in England and Wales [16]. This suggests that something other than package size restrictions, perhaps consumer education, was responsible for the initial decline in the number and percent of events.

Two studies have reported on the lack of adherence in stores to the UK acetaminophen package size restriction legislation [24,25]. In addition, it has been noted that patients and consumers intent on committing suicide can easily visit multiple outlets to obtain large quantities of acetaminophen [25,26].

Multiple studies conducted in Scotland reported that acetaminophen restrictions had no beneficial effect, and, in some cases, had a negative effect on acetaminophen poisoning deaths, hospital discharges following acetaminophen poisoning, acetaminophen overdose based on hospital biochemistry data, admissions to liver transplant units for acetaminophen poisoning, and the proportion of poison center inquiries in which large (>16 grams) acetaminophen doses were reported [27,28,29,30,31,32,33,34]. In an analysis of the period 1990 to 1999, Bateman et al [35] also reported no change in acetaminophen overdose mortality after introduction of package size restrictions in Scotland. Batemen et al [35] reported reductions in acetaminophen overdose hospital discharge after introduction of package size restrictions in Scotland; however, antidepressant overdose and opioid overdose and misuse increased over this same time period. In a subsequent analysis of data from 1995 to 2004 in Scotland by Bateman et al [31], it was reported that the proportion of in-hospital deaths attributed to acetaminophen increased and the proportion of hospital discharges involving acetaminophen in any form increased, except in young men, in Scotland after package size restrictions were introduced. In other studies, short-term reductions in acetaminophen-related deaths, hospital discharges, or emergency admissions were reported, although these trends reversed over time [33,36,37]. Moreover, there were no significant changes in the monthly referral rate to the national Scottish Liver Transplantation Unit for acetaminophen-induced acute liver injury or acetaminophen-induced acute liver failure during the 2.5 years following introduction of package size restrictions when compared with the 5.75 years before restrictions [34]; similar results for varying time periods support these findings [27,32].

The limitations of these studies, including lack of a consensus definition of acetaminophen overdose, limited evaluation period after introduction of the legislation, failure to differentiate between intentional and unintentional overdose, data sources sometimes limited to one or two hospitals, lack of a control or comparison group, and failure to consider changes in overdose epidemiology with other drugs have been presented as barriers to interpretation of the results [38,39,40,41,42]. In addition, the observational nature of these studies makes it difficult to establish a causal link between package size restrictions and changes in the occurrence of acetaminophen overdose.

11.5.3 Restricting Acetaminophen Availability Outside the UK Failed to Have an Appreciable Effect

Studies conducted in Ireland [43,44,45], Australia [46,47], Canada [48], and Denmark [49] have evaluated the effects of changes in acetaminophen availability on acetaminophen overdose and its sequelae. A comparison of data from the UK and

France has also been reported [50]. The majority of these studies reported little or no impact on overdose as the result of changes in the availability of acetaminophen.

11.6 Overview of Rates and Methods of Suicide and Deliberate Self Harm

While it has been reasonably argued that measures used to reduce the incidence of poisoning due to analgesics should be aimed at the root cause rather than the availability of the means for poisoning [4], the impetus for acetaminophen package size restrictions in the UK was to reduce acute intentional overdose as a method of deliberate self-harm and suicide. It is informative to consider the similarities and differences in rates and methods of suicide and suicide attempts in the US compared with the UK as well as with other countries. Differences in rates and/or methods of suicide would affect any potential benefit of package size restrictions in the US. As shown in Table 11-4, suicide rates vary by country and while sometimes reported overall, are often reported separately for men and women. In 2005 in the US, the overall age-standardized suicide rate was 10.9/100,000, with rates of 18.0/100,000 for men and 4.4/100,000 for women [51]. Similar suicide rates were reported in Canada in 2003, with an overall age-standardized rate of 11.3/100,000, with rates of 17.8/100,000 in men and 5.1/100,000 in women [52]. In England and Wales in 2001, age-standardized suicide rates were reported as 13.4/100,000 in men and 4.1/100,000 in women [53]. In Scotland in 2004, crude suicide rates were considerably higher than in England and Wales, Canada, and the US, and were reported as 30.3/100,000 in men and 10.2/100,000 in women [54]. Overall, in the UK in 2006, age-standardized suicide rates were 17.4/100,000 in men and 5.3/100,000 in women [55], and were similar to overall rates in the US in 2005 and in Canada in 2003.

Table 11-4. Age-standardized Rates of Suicides (per 100,000)

Country	Year	Overall	Males	Females
US [51]	2005	10.9	18.0	4.4
Canada [52]	2003	11.3	17.8	5.1
UK [55]	2006	--	17.4	5.3
England and Wales [53]	2001	--	13.4	4.1
Scotland[a] [54]	2004	--	30.3	10.2

a: Crude suicide rates

Any potential positive effect of package size restrictions would likely vary by country, depending on the frequency of self-poisoning with analgesics as a method of suicide. As shown in Table 11-5, methods of suicide vary in frequency of use by country. In the US in 2005, firearms were the most frequent method of suicide and were used in 52.1% of suicides; poisoning was used in 17.6% [51], a subset of which were drug poisoning. When evaluated by gender, the use of firearms was more common in men (57.6%) and poisoning was more common in women (39.1%). In Canada in 2003,

hanging/strangulation/suffocation was the most frequent method and was used in 44% of suicides; poisoning was used in 25% [56]. In contrast, in England and Wales in 2001, the most frequent method was not reported overall; however, poisoning was used in 29.8% (men) to 48.9% (women) of suicides [53]. In Scotland, during the period 1989 to 2002, poisoning was the most frequent method and was used in 32% of suicides [54]. Since poisoning is used in a smaller percentage of suicides in the US compared with the UK, any potential positive impact of analgesic package size restrictions would be reduced in the US.

Table 11-5. Method of Suicide – Percent Distribution

Country	Year	Firearms	Poisoning	Hanging[a]
US [51] (n=32,637)	2005	52.1%	17.6%	22.2%
Males (n=25,907)		57.6%	12.0%	22.7%
Females (n=6730)		31.0%	39.1%	20.2%
Canada [56]	2003	16%	25%	44%
England and Wales [53]	2001	2.9% men 0.6% women	29.8% men 48.9% women	44.2% men 26.7% women
Scotland [54]	1989-2002	2%	32%	27%

a: Hanging, strangulation, and suffocation

Variations in rates and methods of deliberate nonfatal self-harm by country have also been reported. Rates of deliberate self-harm were estimated as 143/100,000 in 1999/2000 in England [21], and 127.17/100,000 to 164.73/100,000 in the US in 2002/2003 [57]. In England, for various reporting periods from 1985 through 2000, the most frequent method of deliberate nonfatal self-harm was self-poisoning, representing 82% to 94% of cases; self-injury, or both self-poisoning and self-injury, and other were the remaining methods [3,20,21,22]. In the US in 2002 to 2003, while self-poisoning was also the most frequent method of nonfatal self-harm, the percent using it was somewhat lower, 66.3% to 73.0% of cases; cutting/piercing accounted for 17.9% to 19.3% of cases [57].

11.7 Potential Unintended Consequences of Package Size Restrictions

The possible unintended consequences of acetaminophen package size and package configuration limitations should be considered, given that only rarely do patients and consumers take an acetaminophen dose that reaches the potential threshold for toxicity. As the mass (in grams) of acetaminophen and aspirin sold decreased following package size restrictions, the mass of ibuprofen sold increased [58]. Increased use of ibuprofen may result in an increase in the incidence of adverse gastrointestinal, renal and other serious adverse effects [59]. Allison and Saag noted the importance of a balanced approach to the regulation of OTC analgesics, and not an isolated focus on acetaminophen, in order to avoid shunting patients from acetaminophen use to NSAID

use [60]. They also noted the greater adverse event concerns with NSAIDs including long-recognized gastrointestinal complications.

Additionally, unintended consequences such as, increased cost and burden to patients and consumers and the healthcare system, increased use of drugs with a less favorable safety profile, and specific burdens to certain patient populations (eg, elderly, individuals with arthritis or other chronic pain conditions) may result in an overall negative impact on patients and consumers and the healthcare system. Restrictions on acetaminophen use may lead to a compensatory increase in overdose with other more toxic drugs for which an antidote is not available, or lead to use of “overdose cocktails” that are more dangerous because of drug-drug interactions and multiple drug toxicities [14,40,61,62]. Such switches from acetaminophen use in overdose have been documented for antidepressants, antipsychotics, sedatives, and ibuprofen [14,16,21].

11.8 Conclusions

- Given the conflicting outcome data in the UK and limitations of the available reports, the evidence for public health benefit from OTC acetaminophen package size or package configuration restrictions is not convincing.
- Data in countries other than the UK generally do not support a positive impact of package size restrictions.
- While package sizes and configurations vary worldwide, within a country there are similar package sizes and configurations for all OTC analgesics.
- The frequency of self-poisoning as a method of suicide is lower in the US compared with the UK.
- If package size restrictions were mandated for selected OTC analgesics, eg, only required for acetaminophen, the potential for and the consequences of patients and consumers switching to other OTC drugs should be considered.
    - Available data suggest that switching from use of acetaminophen to NSAIDs may result in more people dying from NSAID-associated gastrointestinal bleeding and renal failure than those potentially spared from acetaminophen-associated liver injury.

11.9 Reference List

1. Hawton K, Fagg J, Simkin S, et al The epidemiology of attempted suicide in the Oxford area, England (1989-1992). Crisis 1994;15:123-135.

2. Bialas MC, Reid PG, Beck P, et al Changing patterns of self-poisoning in a UK health district. Q J Med 1996;89:893-901.

3. Hawton K, Fagg J, Simkin S, et al Trends in deliberate self-harm in Oxford, 1985-1995. Implications for clinical services and the prevention of suicide. Br J Psychiatry 1997;171:556-560.

4. Mcloone P, Crombie IK. Hospitalisation for deliberate self-poisoning in Scotland from 1981 to 1993: trends in rates and types of drugs used. Br J Psychiatry 1996;169:81-85.

5. Hawton K, Ware C, Mistry H, et al Paracetamol self-poisoning. Characteristics, prevention and harm reduction. Br J Psychiatry 1996;168:43-48.

6. Hawton K, Ware C, Mistry H, et al Why patients choose paracetamol for self poisoning and their knowledge of its dangers. BMJ 1995;310:164.

7. Hawton K. United Kingdom legislation on pack size of analgesics: background, rationale, and effects on suicide and deliberate self-harm. Suicide and Life Threatening Behavior 2002;32:223-229.

8. Hawkins LC, Edwards JN, Dargan PI. Impact of Restricting Paracetamol Pack Sizes on Paracetamol Poisoning in the United Kingdom. A Review of the Literature. Drug Saf 2007;30:465-479.

9. Prince MI, Thomas SH, James OF, et al Reduction in incidence of severe paracetamol poisoning. Lancet 2000;355:2047-2048.

10. Robinson D, Smith AM, Johnston GD. Severity of overdose after restriction of paracetamol availability: retrospective study. BMJ 2000;321:926-927.

11. Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet 2000;355:2048-2049.

12. Langford NJ, Aruna RS, Mutimer D, et al The impact of pack size legislation on paracetamol (acetaminophen) poisoning in the West Midlands (United Kingdom). J Toxicol Clin Toxic 2003;41:419-20.

13. Hawton K, Townsend E, Deeks J, et al Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. BMJ 2001;322:1203-1209.

14. Thomas MR, Jowett NI. Severity of overdose after restriction of paracetamol availability. Restriction has not reduced admissions with self poisoning. BMJ 2001;322:553.

15. Hughes B, Durran A, Langford NJ, et al Paracetamol poisoning - impact of pack size restrictions. J Clin Pharm Ther 2003;28:307-310.

16. Hawton K, Simkin S, Deeks J, et al UK legislation on analgesic packs: before and after study of long term effect on poisonings. BMJ 2004;329:1076-1080.

17. Morgan O, Griffiths C, Majeed A. Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: an observational study. J Public Health (Oxf) 2005;27:19-24.

18. Hawkins LC, Edwards JN, Morgan OW, et al How successful has restricting acetaminophen pack size been in reducing severity of acetaminophen overdose in the UK? Clin Toxicol 2006;44:657-658 (abstract).

19. Morgan O, Hawkins L, Edwards N, et al Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poison center. J Clin Pharm Ther 2007;32:449-455.

20. Hawton K, Hall S, Simkin S, et al Deliberate self-harm in adolescents: a study of characteristics and trends in Oxford, 1990-2000. J Child Psychol Psychiatry. 2003;44:1191-1198.

21. Wilkinson S, Taylor G, Templeton L, et al Admissions to hospital for deliberate self-harm in England 1995-2000: an analysis of Hospital Episode Statistics. J Pubic Health 2002;24:179-183.

22. O'Loughlin S, Sherwood J. A 20-year review of trends in deliberate self-harm in a British town, 1981-2000. Soc Psychiatry Psychiatr Epidemiol 2005;40:446-453.

23. Morgan OW, Griffiths C, Majeed A. interrupted time-series analysis of regulations to reduce paracetamol (acetaminophen) poisoning. PLoS Med 2007;4:e105.

24. Greene SL, Dargan PI, Leman P, et al Paracetamol availability and recent changes in paracetamol poisoning: is the 1998 legislation limiting availability of paracetamol being followed? Postgrad Med J 2006;82:520-523.

25. Norman E, Dhairiwan R, Dargan PI, et al Paracetamol poisoning: can it be prevented? Proc R Coll Physicians Edinb 2001;31:62-65.

26. Cranney M, Cranney J, Stubbs H. Limitation of over the counter sales of paracetamol. Packaging policy is unlikely to achieve its aim of reducing suicide. BMJ 1998;317:1657 (letter).

27. Bathgate AJ, Philip NN, Plevris JN, et al Changing packaging does not reduce serious paracetamol (acetaminophen) poisoning. Hepatology 2000;32:624A (abstract).

28. Laing WJ, Gordon LD, Lee DS, et al Have the new pack size regulations impacted on UK paracetamol overdose? J Toxicol Clin Toxicol 2001;39:301 (abstract).

29. Sheen CL, Dillon JF, Bateman DN, et al The effect on toxicity and healthcare costs on reducing the size of available acetaminophen pack sizes in the Tayside region of Scotland. Gastroenterology 2001;120 (suppl 1):A228 (abstract).

30. Sheen CL, Dillon JF, Bateman DN, et al Paracetamol-related deaths in Scotland, 1994-2000. Br J Clin Pharmacol 2002;54:430-432.

31. Bateman DN, Gorman DR, Bain M, et al Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol 2006;62:573-581.

32. Bates CM, Davidson JS, Simpson KJ. Acetaminophen overdose - a large single centre observational study. Hepatology 2006;44 (4 suppl 1):372A-373A (abstract).

33. Bateman DN, Gorman DR, Bain M, et al Restricting acetaminophen pack size -does it make a difference? J Toxicol Clin Toxicol 2005;43:712 (abstract).

34. Newsome PN, Bathgate AJ, Henderson NC, et al Referral patterns and social deprivation in paracetamol-induced liver injury in Scotland. Lancet 2001;358:1612-1613.

35. Bateman DN, Bain M, Gorman D, et al Changes in paracetamol, antidepressants and opioid poisoning in Scotland during the 1990s. Q J Med 2003;96:125-132.

36. Inglis JH. Restricting sales of paracetamol tablets: effect on deaths and emergency admissions for poisoning in Scotland 1991 - 2002. Scot Med J 2004;49:142-143.

37. Gorman DR, Bain M, Inglis JHC, et al How has legislation restricting paracetamol pack size affected patterns of deprivation related inequalities in self-harm in Scotland? Public Health 2007;121:45-50.

38. Poulin C. Prevention of paracetamol poisoning. Lancet 2000;355:2009-2010.

39. Dargan P, Jones A. Effects of legislation restricting pack sizes of paracetamol on self poisoning. It's too early to tell yet. BMJ 2001;323:633.

40. Isbister G, Balit C. Effects of legislation restricting pack sizes of paracetamol on self poisoning. Authors did not look at effects on all deliberate and accidental self poisoning. BMJ 2001;323:634.

41. Sheen CL, MacDonald TM. Severity of overdose after restriction of paracetamol availability. Study's results conflict with those of other papers. BMJ 2001;322:553-554.

42. Morgan O, Majeed A. Restricting paracetamol in the United Kingdom to reduce poisoning: a systematic review. J Public Health (Oxf) 2005;27:12-18.

43. Laffoy M, Scallan E, Byrne G. Paracetamol availability and overdose in Ireland. Ir Med J 2001;94:212-214.

44. Donohoe E, Tracey JA. Restrictions on sale of paracetamol in Ireland had no impact on the number of tablets ingested in acute deliberate overdose. J Toxicol Clin Toxicol 2000;38:251 (abstract).

45. Donohoe E, Walsh N, Tracey JA. Pack-size legislation reduces severity of paracetamol overdoses in Ireland. Irish J Med Sci. 2006;175:40-42.

46. Balit CR, Isbister GK, Peat J, et al Paracetamol recall: a natural experiment influencing analgesic poisoning. Med J Aust 2002;176:162-165.

47. Kisely SR, Lawrence D, Preston NJ. The effect of recalling paracetamol on hospital admissions for poisoning in Western Australia. Med J Aust 2003;178:72-74.

48. Prior MJ, Cooper K, Cummins P, et al Acetaminophen availability increases in Canada with no increase in the incidence of reports of inpatient hospitalizations with acetaminophen overdose and acute liver toxicity. Am J Ther 2004;11:443-452.

49. Ott P, Dalhoff K, Hansen PB, et al Consumption, overdose and death from analgesics during a period of over-the-counter availability of paracetamol in Denmark. J Intern Med 1990;227:423-428.

50. Gunnell D, Hawton K, Murray V, et al Use of paracetamol for suicide and non-fatal poisoning in the UK and France: are restrictions on availability justified? J Epidemiol Community Health 1997;51:175-179.

51. WISQARS Injury Mortality Reports, 1999-2005. Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC, available online at http://webappa.cdc.gov/sasweb/ncipc/mortrate10_sy.html.

52. Statistics Canada (2006). Mortality, Summary list of causes 2003, Ottawa ON.

53. Brock A, Griffiths C. Trends in suicide by method in England and Wales, 1979 to 2001. National Statistics, Health Statistics Quarterly 20 Winter 2003. available at www.statistics.gov.uk/products/p6725.asp

54. Platt S, Boyle P, Crombie I, et al. The epidemiology of suicide in Scotland 1989-2004: an examination of temporal trends and risk factors at national and local levels. Scottish Executive Social Research 2007. available online at http://www.scotland.gov.uk/Publications/2007/03/01145422/0

55. National Statistics Online. Suicides – Rate in UK men steadies. Available online at http://www.statistics.gov.uk/cci/nugget.asp?id=1092

56. Statistics Canada (2006). Causes of death, 2003, Ottawa ON.

57. Claassen CA, Trivedi MH, Shimizu I, et al. Epidemiology of nonfatal deliberate self-harm in the United States as described in three medical databases. Suicide and Life-Threatening Behavior 2006;36:192-212.

58. Sheen CL, Dillon JF, Bateman DN, et al Paracetamol pack size restriction: the impact on paracetamol poisoning and the over-the-counter supply of paracetamol, aspirin and ibuprofen. Pharmacoepidemiol Drug Saf 2002;11:329-331.

59. Jones AL. Over-the-counter analgesics: a toxicologic perspective. Am J Ther 2002;9:245-257.

60. Allison JJ, Saag KG. Unbalanced regulation of over-the-counter analgesics: the lesser of two evils? Pharmacoepidemiol Drug Saf 2006;15:410-411.

61. Morgan O. Laws limiting the size of paracetamol packs help to prevent overdose. Evidence-Based Healthcare Public Health 2005;9:197-199.

62. Jowett NI. Limitation of over the counter sales of paracetamol. Restriction to 16g will not prevent overdose and is unhelpful for patients with chronic disease. BMJ 1998;317:1657.