

**ITEM 1: MCNEIL'S RESPONSE TO FDA'S PROPOSED LABELING FOR OTC
ACETAMINOPHEN PRODUCTS**

1 INTRODUCTION

McNeil Consumer Healthcare (McNeil) herein submits a response to the Agency's proposed amendment to the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic (IAAA) drug products for Over-the-Counter Human Use (FDA's proposed rule). In developing its proposals, FDA contends that it relied on discussions and recommendations made by the Nonprescription Drugs Advisory Committee (NDAC) after the meeting on September 19 and 20, 2002, and other available information. McNeil's comments on FDA's proposed labeling amendments for over-the-counter (OTC) acetaminophen-containing products are based on a broad review of the currently available data and provide scientifically appropriate modifications to several of the FDA's labeling proposals.

Item I, McNeil's Response to FDA's proposed labeling for OTC acetaminophen products, is organized to reflect the organization of FDA's proposed rule, where possible. In the beginning of each section, relevant FDA comments are provided, followed by McNeil's position, and key points for the section. This is followed by an in-depth discussion of the data, including presentation of new and additional analyses provided by McNeil. The following topics are included in Item 1:

- Section 2: A presentation of McNeil's general comments on FDA's proposed rule and specific comments on FDA's proposed label revisions for OTC acetaminophen-containing products.
- Section 3: A review of data related to the threshold for acetaminophen overdose toxicity.
- Section 4: A review of available estimates of acute liver failure; a critique and further analysis of case reports/case series and national databases cited in FDA's proposed rule; and a discussion of areas of consideration for future monitoring of the effect of any labeling changes.
- Section 5: A review of experimental data on the role of metabolism on liver safety in liver disease and understanding complex alcohol interactions.
- Section 6: A summary of published and new clinical acetaminophen metabolism data in adults and children with liver disease.
- Section 7: A summary of studies demonstrating the proven safety of therapeutic doses of acetaminophen in individuals who consume alcohol.
- Section 8: A review of consumer medication use in the US and a summary of McNeil's labeling and educational initiatives.

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2 MCNEIL'S COMMENTS ON FDA'S PROPOSALS FOR LABELING OF OTC ACETAMINOPHEN PRODUCTS

McNeil markets a comprehensive line of 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. As the manufacturer of these products, McNeil is committed to encouraging scientifically appropriate and adequate labeling, which includes consistent, clear, and appropriate language for consumer use.

2.1 McNeil's General Comments on FDA's Proposed Rule

In response to FDA's proposed rule [71 FR 77314] of December 26, 2006 [herein referred to as FDA's proposed rule], McNeil provides comments based on the most currently available science, which includes new scientific data from clinical and metabolism studies, as well as new analyses of published literature and epidemiological databases, as provided in Item 1, Sections 3 to 7 of this response.

McNeil concurs with FDA's statements [71 FR 77315] that OTC acetaminophen-containing products:

- are safe and effective when labeled appropriately and used as directed
- benefit tens of millions of consumers every year
- should continue to be accessible to consumers in the OTC setting
- have long been effective for the intermittent treatment of minor aches and pains and fever

FDA states in its proposed rule, "at their (ie, OTC internal analgesic products) recommended OTC doses, these products are only rarely associated with serious adverse events relative to the number of consumers who use these products." [71 FR 77315] Elsewhere in the proposed rule, FDA specifies liver injury as the "serious side effects" that can occur with acetaminophen [71 FR 77331].

McNeil disagrees with these statements because they inaccurately reflect the currently available science, which shows hepatic injury can occur following substantial acetaminophen overdose, but does not show a risk of hepatic injury with the maximum labeled daily dose of acetaminophen, regardless of population (Item 1, Sections 3 through

7). While there exist retrospective case reports of serious hepatic events reported to involve acetaminophen-containing products, the information reported from these cases are inherently of limited value and provide no reliable evidence of toxicity at recommended OTC doses of acetaminophen (Item 1, Section 3). McNeil agrees with FDA's tentative conclusions that "when taken in excess amounts, acetaminophen can cause liver injury" as well as the statement that notes the rarity of such events by stating that, "when compared to the extensive use of OTC acetaminophen drug products, the incidence of injury appears relatively low." [71 FR 77331]

2.2 McNeil's Specific Comments on FDA's Proposed Labeling

Based on a broad review of the available data, McNeil provides scientifically appropriate modifications to several of FDA's labeling proposals. Additionally, McNeil provides comments on additional opportunities that may help to minimize consumer misuse of OTC acetaminophen-containing products and prescription acetaminophen-combination products.

2.2.1 FDA Proposal - Prominence of "acetaminophen" on the OTC Principle Display Panel (PDP)

FDA proposes that the name "acetaminophen" appearing on the PDP of the OTC primary container for all acetaminophen-containing products should be enhanced to allow consumers to better identify acetaminophen-containing products.

FDA's specific proposals to help consumers recognize "acetaminophen" as an ingredient in OTC products are as follows:

- "The presence of acetaminophen in the product must be prominently stated on the PDP"
- "The presence of acetaminophen must appear as part of the established name of the drug"
- "Combination products containing acetaminophen and a non-analgesic ingredient(s) (eg, cough-cold) must include the name "acetaminophen" and the names of the other active ingredients in the product on the PDP. Only the name "acetaminophen" must appear highlighted"

McNeil agrees with FDA that it is important to help consumers more easily identify acetaminophen as an active ingredient in acetaminophen-containing products, as well as

other active ingredients in OTC products. As such, in 2002, McNeil voluntarily increased the prominence of “acetaminophen” on the PDP for its single- and combination-ingredient adult and pediatric Tylenol acetaminophen products.

2.2.2 FDA Proposal – Alcohol Warning

FDA proposes to remove the alcohol warning currently required for all OTC IAAA drug products in § 201.322 (21 CFR 201.322). FDA’s current alcohol warning for OTC acetaminophen products is as follows:

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Instead, the Agency proposes to incorporate an alcohol warning as part of FDA’s proposed new liver warning for acetaminophen. In this regard, FDA’s proposed rule states, “FDA has combined this information (ie, separate alcohol and liver warnings) because it is interrelated and a shorter warning saves label space on products that already contain extensive labeling information. FDA believes that two, separate warnings may be less likely to be read and understood by consumers.” [71 FR 77331]

2.2.2.1 McNeil’s Proposal: Alcohol Warning Is Not Necessary

Based on currently available science, including results from new prospective double-blind, placebo-controlled, randomized clinical studies, an alcohol warning for OTC acetaminophen products is not necessary for the following reasons:

- In its original rulemaking for the current alcohol warning for OTC acetaminophen-containing products in 1997, FDA relied only upon the then-available retrospective case reports to cite a risk of hepatotoxicity in heavy users of alcohol, some of which reportedly ingested recommended doses of acetaminophen [62 FR 61045]. McNeil’s review of currently available science, including results from new prospective, double-blind, placebo-controlled, randomized clinical studies, supports the fact that individuals with a history of alcohol use can safely take the maximum labeled daily dose of acetaminophen and that the only risk of hepatotoxicity is when taking more than the recommended dose (overdose) irrespective of a history of alcohol use (Item 1, Sections 3 and 7). Both FDA’s current alcohol warning and

FDA's proposed alcohol warning (as part of a new liver warning) specifically and inappropriately place an alcohol warning in the context of recommended use and dosing of acetaminophen, when neither of FDA's warnings are consistent with the currently available science. In addition, the risk of acetaminophen-related liver damage is an overdose risk that applies not just to those individuals who use or abuse alcohol, but to the general population as well. Therefore, it is not necessary or appropriate to specifically call out those individuals who use or abuse alcohol.

- FDA does not provide any evidence to support their rationale for incorporating an alcohol warning as part of the new liver warning. McNeil does not agree with the Agency's assertion that there is a need to merge the two different warnings simply for the sake of brevity, when there is a greater need to ensure accuracy and clarity based on available science. Inappropriately combining such information will mislead consumers and result in greater confusion.

If FDA deems that some type of alcohol warning is needed on OTC acetaminophen-containing products, it must be modified to precisely reflect the available scientific evidence of a potential risk from overdose:

McNeil Proposal –Modification of FDA's Current Alcohol Warning

"Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Taking more than the recommended dose (overdose) of acetaminophen may cause liver damage."

2.2.3 FDA Proposal - Liver Warning

In the rulemaking, "FDA has determined that adding a liver warning is necessary for safe and effective use of the drug (acetaminophen) and to reduce the number of unintentional overdoses. Thus, FDA is proposing a "liver warning" stating use factors that could lead to liver injury." Additionally, the Agency recommends incorporating an alcohol warning as part of a proposed new liver warning for acetaminophen in an attempt to save label space [71 FR 77331].

FDA's proposals for a new liver warning for adult and pediatric OTC acetaminophen products are as follows:

Products Labeled for Adults Only

Liver warning: This product contains acetaminophen. Severe liver damage may occur if you take

- more than (insert maximum number of daily dosage units) in 24 hours
- with other drugs containing acetaminophen
- 3 or more alcoholic drinks every day while using this product.

Products Labeled Only For Children <12 Years of Age

Liver warning: This product contains acetaminophen. Severe liver damage may occur if the child takes

- more than 5 doses in 24 hours
- with other drugs containing acetaminophen

Products Labeled For Adults and Children <12 Years of Age

Liver warning: This product contains acetaminophen. Severe liver damage may occur if

- adult takes more than (insert maximum number of daily dosage units in 24 hours)
- child takes more than 5 doses in 24 hours
- taken with other drugs containing acetaminophen
- adult has 3 or more alcoholic drinks every day while using this product

2.2.3.1 McNeil Proposal - Liver Warning

Having considered FDA's proposal and the scientific evidence that acetaminophen can cause liver injury when taken in amounts exceeding the recommended dose (overdose), McNeil agrees that FDA's proposal to add a liver warning is an acceptable revision, but disagrees with FDA's proposed wording, which inappropriately implies a risk with recommended use and dosing of acetaminophen. Further modifications to FDA's proposal are warranted so that the liver warning more precisely reflects the scientific evidence and communicates the potential risk appropriately.

McNeil Proposal – Liver Warning (Products Labeled for Adults Only)

“Liver warning: This product contains acetaminophen. Liver damage may occur if you take more than the recommended dose (overdose).

Do not:

- take more than 8 caplets in 24 hours

- use with other drugs containing acetaminophen”

For products labeled for both adults and children <12 years of age, the bulleted text, “Give the child more than 5 doses in 24 hours” would be added in McNeil’s proposal. For products labeled only for children <12 years of age, the bulleted text, “Give the child more than 5 doses in 24 hours” would be added to replace “Take more than 8 caplets in 24 hours” in McNeil’s proposal.

McNeil’s proposed language explicitly informs consumers that the risk behavior is from taking more than the recommended dose (overdose) and directs them to avoid situations that may result in taking too much of the specific acetaminophen product, or using it with other products that also contain acetaminophen, which may result in exceeding the recommended dose (overdose). McNeil’s proposed language also reflects NDAC discussions that it was important that the message incorporate a statement such as “do not take more” or “do not exceed the recommended dose.” [71 FR 77324]

Furthermore, McNeil disagrees with FDA’s proposal to use the term “severe” to qualify liver damage, as the term “severe” is not necessary for a liver warning for acetaminophen. In describing events, use of modifiers such as “severe” across the category of OTC analgesics must be consistently applied so that healthcare professionals and consumers can make appropriate and informed choices about which OTC analgesic product to recommend/take. The modifier “severe” is not used in the language of FDA’s stomach bleeding warning on OTC NSAID products, where it would be more appropriate, relatively. For these reasons, the term “severe” should be removed from FDA’s proposed liver warning for OTC acetaminophen-containing products.

Additionally, FDA proposes to incorporate an alcohol warning as part of FDA’s proposed new liver warning for acetaminophen. In this regard, FDA’s proposed rule states, “FDA has combined this information (ie, separate alcohol and liver warnings) because it is interrelated and a shorter warning saves label space on products that already contain extensive labeling information [71 FR 77331]. It is McNeil’s position that an alcohol warning for OTC acetaminophen products is not necessary, whether it be FDA’s current warning or FDA’s proposal to incorporate an alcohol warning as part of a new liver warning in an attempt to save label space. For a detailed discussion of McNeil’s proposal with regards to an alcohol warning for OTC acetaminophen-containing products, please refer to Item 1, Section 2.2.2 of this response.

2.2.4 FDA Proposal - Concomitant Use Warning

FDA proposes label statements to help consumers avoid concomitant use of more than one acetaminophen-containing product and when to talk to a healthcare professional:

- Do not use with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure.

2.2.4.1 McNeil Proposal – Concomitant Use Warning

McNeil agrees, in general, with FDA's proposal because evidence cited by FDA in FDA's proposed rule [71 FR 77323] and elsewhere [1] identifies reports of what appears to be the unintentional use of multiple acetaminophen-containing products, including OTC and prescription products, to such a degree that the combined use potentially results in overdose with the potential for toxicity.

McNeil disagrees with FDA's proposed wording because it does not provide enough information about what to ask the doctor or pharmacist. In order to more clearly identify for the consumer what question they should ask their doctor or pharmacist, McNeil recommends the following alternate language be used in place of the FDA's proposed wording.

McNeil's Proposal - Concomitant Use Warning

"Do not use with any other drug containing acetaminophen (prescription or non-prescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist."

2.2.5 FDA Proposal - Preexisting Liver Disease Warning

In FDA's proposed rule, FDA notes that NDAC briefly discussed preexisting liver disease as a potential risk factor for acetaminophen toxicity in September 2002, but concluded that there were not sufficient data to make specific recommendations. After the 2002 NDAC meeting, FDA conducted a literature review (1966 to January 2003) and determined that certain factors may place patients with preexisting liver disease at greater risk for acetaminophen toxicity. FDA has reconsidered its previous position on this issue and now states that the current evidence supports a warning [71 FR 77328].

FDA proposes an additional warning to alert patients with chronic liver disease to ask their doctor before using acetaminophen:

- Ask a doctor before use if you have liver disease. (products labeled for adults only)
- Ask a doctor before use if the child has liver disease. (products labeled for children < 12 years of age only)
- Ask a doctor before use if the user has liver disease (products labeled for adults and children <12 years of age)

2.2.5.1 McNeil Proposal – Preexisting Liver Disease Warning Is Not Necessary

McNeil disagrees with FDA's tentative conclusion that preexisting liver disease is a risk factor for developing acetaminophen hepatotoxicity. The experimental and clinical data that FDA reviewed and summarized in FDA's proposed rule are incomplete and do not support the supposition that recommended OTC doses of acetaminophen result in hepatotoxicity in individuals with liver disease. Based on the most currently available science (Item 1, Sections 5 through 7), stable chronic liver disease, in the presence or absence of alcohol, does not result in the development of hepatotoxicity with maximum-labeled daily doses of acetaminophen.

In Item 1, Sections 5 and 6, McNeil provides an extensive analysis of the literature published up to April 2007 on experimental and clinical metabolism studies of acetaminophen and liver disease, and new metabolism data from a recently completed study in hepatic-impaired adults sponsored by McNeil. In our analysis of the literature, new and more sophisticated evidence of the role of critical cytochrome P450 isoforms (CYP2E1), hepatocellular glutathione homeostasis, and glucuronyltransferase systems shows that the suppositions regarding risk in individuals with preexisting liver disease are theoretical in nature. These experimental and scientific data do not support the hypothesis that individuals with liver disease develop hepatotoxicity at recommended doses of acetaminophen.

McNeil's position is also supported by prospective scientific and clinical evidence from several acetaminophen metabolism studies in adults and children with liver disease of varying severity and etiology, including a recently completed study in hepatic-impaired adults sponsored by McNeil (Item 1, Section 6). Based on the most currently available science, the addition of FDA's proposed labeling text: "Ask a doctor before use if you have liver disease" is not warranted.

However, should FDA continue to assert that individuals diagnosed with liver disease be alerted to talk to their doctor before using acetaminophen, this warning should be appropriately considered for OTC NSAID products as discussed in Item 3 of this response because acetaminophen is the recommended analgesic of choice in individuals with liver disease and OTC NSAIDs should be used with caution in this subset population. Also, in the proposed rule, FDA cites evidence that individuals with liver dysfunction with ascites are at risk for a variety of adverse renal effects from OTC NSAIDs [71 FR 77331], but fails to apply a preexisting liver disease warning on OTC NSAID products. If the OTC NSAID standard were used, it would preclude such a warning on OTC acetaminophen products as well.

2.2.6 FDA Proposal - *“This product does not contain directions or warnings for adult use”*

McNeil notes FDA’s stated observation in FDA’s proposed rule that products labeled “for children only” are sometimes used by adults who cannot take solid oral dosage forms or who are taking a product marketed in children’s strengths [71 FR 77333]. As such, McNeil agrees with FDA’s proposal to include the above statement on the label for acetaminophen products labeled for children only. McNeil requests that FDA provide the flexibility to place this warning in the “Do not use” section of the OTC Drug Facts, instead of only in the “Directions” section of the children’s product because the Directions section of pediatric OTC products are often lengthy and crowded with information.

2.3 Additional Opportunities to Minimize Unintentional Acetaminophen Overdose

Evidence identified by FDA describes concerns with unintentional acetaminophen overdose involving prescription acetaminophen-combination products and with the lack of OTC pediatric dosing information for children <2 years of age. In this section, McNeil provides specific suggestions to FDA.

2.3.1 *Inadequate information on container labels of prescription acetaminophen-combination products*

For prescription acetaminophen-combination products, FDA has identified the following from among reasons for unintentional overdose in adults, “the failure of prescription container labels to list acetaminophen as an ingredient” and “container labeling for

prescription products, dispensed by a pharmacy, that may not clearly identify acetaminophen as one of the active ingredients and the maximum daily acetaminophen dose limit” [1, 2].

In this proposed rule, FDA also cites data involving prescription acetaminophen combination products. In an FDA analysis of reports of hepatotoxicity coincident with acetaminophen use from FDA’s adverse event reporting system (AERS), 33% of adult cases reportedly involved the use of a narcotic-acetaminophen prescription product. Approximately 25% of all adult cases reported use of more than one acetaminophen product, with a narcotic-acetaminophen prescription product in combination with an OTC product containing acetaminophen being used more often than any other combination of acetaminophen products [71 FR 77320-21].

FDA is silent in this rulemaking about supporting or initiating possible actions to improve labels of prescription containers and labeling for prescription acetaminophen-combination products. McNeil encourages FDA to address this public health concern. McNeil also suggests that FDA, Pharmacy and Medical Associations, as well as other interested stakeholders, work to improve container labels of prescription combination products containing acetaminophen to increase consumer understanding that prescription acetaminophen-containing products contain the active ingredient “acetaminophen”, and to improve education of healthcare professionals on this matter.

2.3.2 Lack of standardized pediatric acetaminophen dosing information, especially for infants

In FDA’s proposed rule, FDA cited pediatric cases in FDA’s Adverse Events Reporting System (AERS) (reported with acetaminophen products) of instances of misinterpretation of instructions provided by a healthcare professional and notes that NDAC expressed concern about the lack of standardized pediatric dosage information, especially for infants <2 years of age [71 FR 77320 and 77332].

As a manufacturer of pediatric OTC analgesics products, McNeil submitted to FDA on February 1, 1999, a Citizen Petition (Docket 77N-0094) to amend the tentative final monograph to expand OTC consumer information for acetaminophen dosing for children <2 years of age [3]. McNeil’s Petition’s rationale includes:

- For most caregivers and healthcare professionals, the lack of available dosing information on the label is inconvenient and distressing. It produces tens of thousands of unnecessary telephone calls to healthcare professionals. It creates anxiety and frustration on the part of caregivers seeking dosing information.
- In some cases, this inconvenience can have serious medical consequences. Almost all of the acetaminophen overdoses reported in small children involve a miscommunication between the healthcare professional and caregiver, with the healthcare professional recommending a dose that the caregiver cannot verify by looking at the label. At an FDA NDAC meeting in 1997, McNeil carefully delineated the nature of these cases.
- If dosing information for this subset population is made available on the label, both the caregiver and healthcare professional will know what the proper dose of the specific product and formulation should be.

In April 2001, FDA acknowledged receipt of McNeil's Citizen Petition. In August 2001, McNeil provided additional information to FDA. At the 2002 NDAC meeting, FDA commented that it had prepared a response to this Citizen Petition. To date, FDA has provided no substantive response and, once again, McNeil strongly urges FDA to act on our Citizen Petition and provide OTC acetaminophen dosing directions for children under two years of age on the OTC acetaminophen consumer package, similar to the availability of dosing directions for children under two years of age already on OTC ibuprofen products.

2.4 Reference List

- 1 FDA Science Background: Safety Concerns Associated with Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use. January 22, 2004. Available at: <http://www.fda.gov/cder/drug/analgesics/SciencePaper.htm>. Accessed May 4, 2007.
- 2 FDA Letter to State Boards of Pharmacy. Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity. January 22, 2004. Available at: <http://www.fda.gov/cder/drug/analgesics/letter.htm>. Accessed May 4, 2007
- 3 McNeil Citizen Petition, Docket Number 77N-0094, Labeling for dosing of acetaminophen in children under age two, Dated 2/1/99, Amended 8/15/2001.

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3 THRESHOLD FOR ACETAMINOPHEN OVERDOSE TOXICITY

3.1 FDA Comments from the Proposed Rule

In Part A, Safe and Effective Daily Acetaminophen Dose, of Section VII of the FDA Proposed Rule [71 FR 77335], FDA states, “The current information on unintentional overdose suggests that the margin of safety may be less than originally determined.” FDA further states, “The data on liver failure presented by Dr. Lee at the September 2002 NDAC meeting and the adverse event reports in the FDA AERS data suggest daily doses less than 10 g, ingested on consecutive days, presents a risk for liver injury in some individuals”.

3.2 McNeil’s Position

McNeil does not agree with FDA’s assessment, based on available data that do not support that repeated suprathreshold ingestions of acetaminophen of less than 10 g/day present a risk for liver injury. Instead, prospective data indicate that the threshold for toxicity is a repeated suprathreshold ingestion of acetaminophen of at least 10 g/day for at least two to three days.

3.3 Key Points Supported By Scientific and Medical Data

- Acetaminophen taken at maximum labeled daily doses of up to 4 g/day is well tolerated. Ingestion of more than 4 g in a 24 hour period is defined as an overdose. Ingestion of more than 4 g in an eight hour period is defined as an acute overdose. Ingestion of more than 4 g/day in divided doses is defined as a repeated suprathreshold ingestion. However, taking more than the maximum labeled daily dose (overdose) in any one of these scenarios does not define the threshold for toxicity.
- New data from a pharmacokinetic/metabolism study demonstrate the safety of repeated suprathreshold doses of 6 or 8 g/day in healthy volunteers, where doses up to 8 g/day for three days were given without evidence of hepatotoxicity. In fact, in this study, repeat dosing was shown to increase the liver’s ability to form the nontoxic glucuronide metabolite, while not increasing the production of thiol metabolites (ie, not increasing the production of the toxic intermediate).
- A prospective, observational case series of repeated suprathreshold overdoses indicate that the threshold for toxicity is a repeated suprathreshold ingestion of at

least 10 g/day for at least two-to-three days. In this case series, subjects who reported taking repeated suprathreshold ingestion showed:

- no evidence of an elevation in aspartate aminotransferase (AST < 50); the average reported dose was 10.6 g/day (CI: 9.4 to 11.7) taken for a median duration of 37 hours;
 - evidence of some level of AST elevation (AST ≥ 50 <1000 IU/L); the average reported dose was 11.7 g/day (CI: 9.6 to 13.8) taken for a median duration of 48 hours; and
 - evidence of hepatotoxicity (AST >1000 IU/L); the average reported dose was 12.6 g/day (CI: 10.3 to 14.9) taken for a median duration of 72 hours.
- With regard to making comparisons between toxicity from acute overdoses and toxicity from repeated suprathreshold overdoses, prospective pharmacokinetic and metabolism studies indicate that the hepatotoxic potential would be less when the overdose is divided over an entire day (repeated suprathreshold overdose) than when the overdose is taken all at once (acute overdose).

3.4 Overdose and Toxicity

3.4.1 Situations of Potential Acetaminophen Overdose and Misadministration

It is important in the process of reviewing data, with regard to both causes and consequences and for conducting an appropriate risk assessment, that careful definitions of product use or misuse are used. [Table 3.1](#) summarizes terms commonly used to describe overdose situations that are frequently seen in the acetaminophen literature. It also specifies terminology that McNeil will be using in this document to define specific types of use, misuse, and overdose.

Table 3.1 Standardized Terms Used to Describe Types of Overdose or Appropriate Therapeutic Use

Common Terms Used to Describe Overdose	Standardized Term Used in This Section
Intentional overdose; Purposeful ingestion; Suicide Attempt; Suicide gesture; Intentional Poisoning; Poisoning	Acute Intentional Overdose in Adults: Suicides or Gestures
Accidental overdose; Accidental ingestion; Exposure; Poisoning	Acute Accidental Overdose in Children: Exploratory Ingestions or Exposures

Table 3.1 Standardized Terms Used to Describe Types of Overdose or Appropriate Therapeutic Use

Common Terms Used to Describe Overdose	Standardized Term Used in This Section
Accidental overdose; Unintentional overdose; Chronic overdose; Chronic misuse; Therapeutic misuse; Therapeutic error; Therapeutic misadventure; Poisoning	Repeated Supratherapeutic Overdose in Adults: Doses Exceeding 4g/day
Accidental overdose; Unintentional overdose; Chronic overdose; Chronic misuse; Therapeutic misuse; Therapeutic error; Therapeutic misadventure; Inadvertent Overdose; Poisoning	Repeated Supratherapeutic Overdose in Children: Doses Exceeding 75mg/kg/day
Dosing Error; Single dose overdose; Therapeutic error; Exposure; Poisoning	Dosing Error without Overdose: Doses do not exceed 4g/day (or 75mg/kg/day)
Therapeutic use; Therapeutic ingestion; Chronic use	Appropriate Therapeutic Use, Recommended Dose, Therapeutic Doses, Maximum Labeled Daily Dose: Doses do not exceed 4g/day (or 75mg/kg/day)

3.5 Definition of Potentially Toxic Doses

The maximum labeled daily dose for acetaminophen is 4 g/day. Ingestion of more than 4 g in a 24-hour period is defined as an overdose. Ingestion of more than 4 g in an eight-hour period is defined as an acute overdose. Ingestion of more than 4 g/day in divided doses is defined as a repeated supratherapeutic ingestion. However, taking more than the recommended maximum daily dose (overdose) in any one of these scenarios does not define the threshold for toxicity.

3.5.1 Acute Intentional Overdose in Adults – Suicide Gestures or Attempts

Acute intentional overdose in adults and adolescents, either as a suicide gesture or attempt and whether successful or unsuccessful, cause most of the serious cases of acetaminophen hepatotoxicity. The actual frequency of suicide as a reason for overdose may be higher than reported because suicidal intent is difficult to confirm and disclosure of suicidal intent may be of concern given possible repercussions, such as loss of insurance coverage, privacy, social stigma, and family impact.

Acetaminophen overdose can occur following a single ingestion or repeated ingestions exceeding the maximum labeled daily dose. Acute acetaminophen overdose is defined as an ingestion of an amount of acetaminophen that is greater than the maximum-labeled daily dose within a period of eight hours or less. In adults and adolescents, hepatic injury has been reported to occur following ingestion of greater than 7.5 to 10 g of acetaminophen (ie, 24 regular-strength or 15 extra-strength caplets or tablets) within a period of eight hours or less. Other medical toxicologists state that an acute acetaminophen overdose of approximately 15 g is thought to be the threshold for causing toxicity in adults [1,2]. In adults and adolescents, fatalities are infrequent (less than 3% to 4% of untreated cases) with acute overdoses less than 15 g (ie, 45 regular-strength or 30-extra-strength caplets or tablets).

3.5.1.1 Single-Dose Pharmacokinetic Studies in Volunteers Given up to Nine Grams as a Acute Overdose

Data from prospective clinical studies in which acetaminophen was given to volunteers in excess of maximum labeled doses¹ provide an estimate of what degree of overdose can be tolerated without developing hepatic injury. These studies were designed to simulate acute overdoses² 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 [3,4] and assess various overdose interventions [5,6,7,8,9]. Only pharmacokinetic data for the control groups without absorption interventions (eg, activated charcoal and lavage) are included in this section, because they provide information about those instances when an individual takes more than a 1 g dose of acetaminophen.

Acetaminophen absorption after an acute single dose of 75 mg/kg from either immediate-release or extended-release caplets was assessed in two studies of healthy men and women [3,4]. In both studies, the doses (3.8 to 7.2 g, and 4.2 to 7.8 g) were well tolerated, and adverse events (nausea, headache, and light-headedness) were minor and transient. In another study, a single dose of 5 g was administered to healthy adults on four occasions, three of which included co-administration of activated charcoal as an intervention [5].

¹ Therapeutic doses of 0.65 and 1g 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).

² 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.

Similar studies of 3.6 or 4 g single doses of acetaminophen were administered on four occasions. Changes in absorption were determined when activated charcoal, without [8] and with gastric lavage [6,9], was co-administered with the dose. The doses in all these studies were well tolerated.

The effect of different body positions on absorption was assessed in healthy men and women, who ingested 80 mg/kg (4.1 to 9.1 g) on five occasions with a three-day washout between each administration [7]. Subjects were required to swallow within 60 seconds the entire quantity of tablets, which ranged from 26 to 57 tablets of 160-mg acetaminophen each. These acute overdoses were well tolerated, with no adverse events or discontinuations reported.

Mean data for the control groups are summarized in [Table 3.2](#), and show that acetaminophen pharmacokinetics following acute overdose are similar to those following the maximum-labeled single dose (1 g). [Figure 3.1](#) depicts mean pharmacokinetic profiles for the 5.6 g (75 mg/kg) acetaminophen dose [4] and the maximum-labeled single dose of 1 g (15 mg/kg) [10]. These profiles are drawn relative to the standard lines on the Rumack-Matthew acetaminophen nomogram that are used to manage acute acetaminophen overdose: the 4-hour 150-mcg/mL treatment line and 200-mcg/mL risk line. At all times during the study, the mean plasma concentrations for both the 15 mg/kg and 75 mg/kg doses are well below the lines of the nomogram, which further supports the safety findings. No patterns in the pharmacokinetic curves indicative of significant metabolic saturation were found at these doses.

Overall, 80 subjects in these prospective studies ingested from 2.8 to 9.1 g of acetaminophen on more than one occasion, which totaled 152 exposures of single supratherapeutic doses. An additional 120 exposures included co-administration with activated charcoal. These data demonstrate that single doses of up to 9 grams taken as an acute overdose have been tolerated without adverse effects in healthy adults.

Table 3.2. Mean (sd) Pharmacokinetics Data for Doses Up to Nine Grams

Citation	Study Description	Gender M / F	Weight (kg)	Dose (g) (Range)	AUC _{INF} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C _{MAX} ($\mu\text{g}/\text{mL}$)	T _{MAX} (h)	t _{1/2} (h)
[9]	Control ^a vs Charcoal/ Lavage	5 / 7	71.8	3.6 ^b 2.8 to 5.3	190	42	1.7	2.2
[8]	Control ^a vs Charcoal	7 / 3	77.4	4.0 (na)	221 (54)	66 (27)	--	2.3 (0.6)
[6]	Control ^a vs Charcoal/ Lavage	12	--	4.0 (na)	--	70 (7.4)	--	--
[5]	Control ^a vs Charcoal	10 / 0	73	5.0 (na)	347 (73)	64 (14)	1.4 (0.52)	2.6 (0.3)
[4]	BA Comparative ^c	7 / 7	67.8	5.6 ^b 4.2 to 7.8	419 (98)	100 (25)	0.9 (0.6)	2.6 (0.4)
[3]	BA Comparative ^c	7 / 3	73	5.7 ^b 3.8 to 7.2	432 (132)	94 (24)	0.8 (0.5)	2.6 (0.9)
[7]	BA in Five Body Positions	6 / 6	--	6.1 ^b 4.1 to 9.1	--	--	--	--

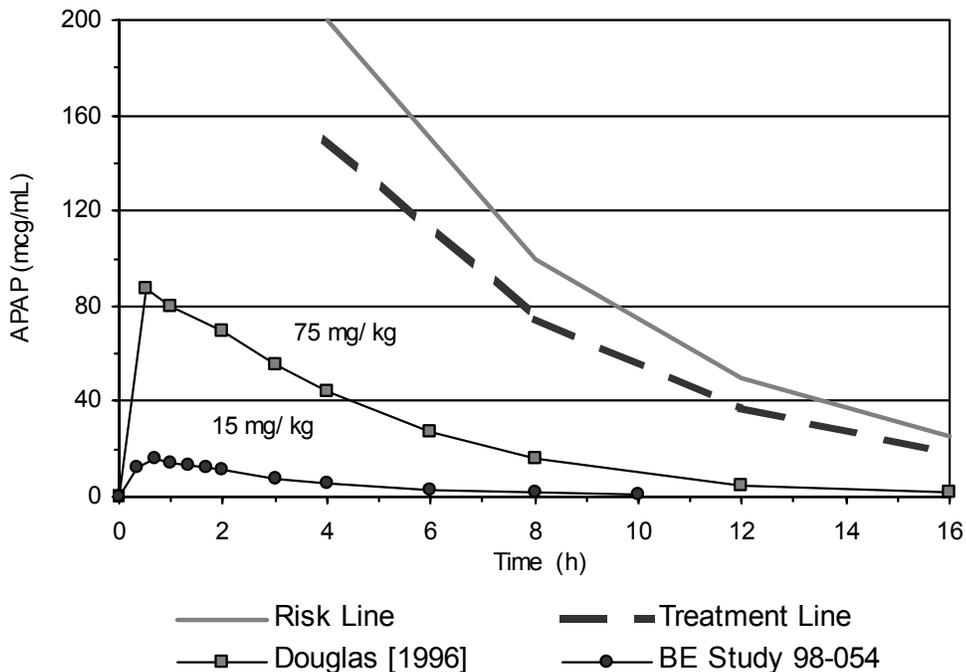
a: control group data reported.

b: study average dose.

c: immediate-release data reported.

Abbreviations: BA = bioavailability; na = not applicable

Figure 3.1 Mean Data for a Standard (1 g, 15 mg/kg) and Higher (5.6 g, 75 mg/kg) Dose Relative to Risk Line (200 mcg/mL at 4 hrs) and Treatment Line (150 mcg/mL at 4 hrs) of the Acetaminophen Nomogram



3.5.2 Acute Accidental Overdose in the Pediatric Population

Acute accidental ingestion or overdose in young children generally occurs because small exploratory children get into unattended medicines and ingest them. Because of the widespread availability of acetaminophen in US households, there are a large number of acute accidental ingestions in the pediatric population each year. Not all ingestions result in an overdose, so the reports are generally referred to as exposures. 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 pediatric ingestions of adult acetaminophen dosage forms infrequently produces 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, in children, an acute accidental overdose of greater than 200 mg/kg is thought to be the threshold for toxicity [11,12].

3.5.3 Repeated Supratherapeutic Overdose 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 maximal labeled daily dose 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.

With regard to making comparisons between toxicity from acute overdoses and toxicity from repeated supratherapeutic overdoses, prospective pharmacokinetic and metabolism studies indicate that the hepatotoxic potential would 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). 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 hour³ to the pool available to detoxify N-acetyl-p-benzoquinoneimine (NAPQI), the reactive acetaminophen metabolite [13,14,15]. Acetaminophen plasma concentrations would also be expected to reach higher levels following most acute overdoses than following most repeated supratherapeutic overdoses.

³ Estimate for a 70 kg person.

Additionally, exposure to several repeat doses of 1, 1.5, and 2 g acetaminophen was recently discovered to induce UDP-glucuronyltransferases, which increases the liver's ability to form the nontoxic glucuronide metabolite while not increasing the production of thiol metabolites via the toxic intermediate [16,17].

A few prospective studies evaluated situations where doses of acetaminophen greater than the maximum labeled daily dose have been taken. Many individuals who take repeated supratherapeutic overdoses do not develop hepatotoxicity. Importantly, estimates of the threshold dose for toxicity should be based on those few studies, rather than retrospective case reports and case series in which the true dose of acetaminophen ingested is unknown.

3.5.3.1 Prospective Clinical Studies of Hepatotoxic Potential for Repeated Supratherapeutic Doses of Acetaminophen

The safety of repeated supratherapeutic doses of 6 or 8 g/day has been demonstrated in healthy volunteers [16,17,18]. The multiple-dose pharmacokinetic study has a randomized, double-blind, placebo-controlled, parallel-group design with three dosing regimens. Healthy subjects received repeated doses of acetaminophen (4 then 6 g/day or 4 then 8 g/day) or placebo. The disposition of acetaminophen and its metabolites, and the tolerability of acetaminophen doses greater than the maximum labeled daily dose over three days of continuous use were characterized [17]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities measured throughout the study were consistent across the 4, 6, and 8 g/day acetaminophen dose levels and with placebo. Serum aminotransferase activities did not exceed the upper limit of the reference range (ULRR), except for one subject with an AST of 43 U/L (ULRR, 42 IU/L), which was not considered clinically significant [18]. See [Table 3.3](#) for details of measured liver tests by study group and dosing period.

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 8 g/day and three randomized to placebo); dizziness (five subjects: three receiving 4 g/day, one receiving 8 g/day, and one randomized to placebo); and nausea (five subjects: one receiving 4 g/day, one while receiving both 4 and 6 g/day, one receiving 8 g/day, and two randomized to placebo). Overall, in this multiple-dose pharmacokinetics study of 4, 6, and 8 g/day of acetaminophen for three days, several

Table 3.3 Mean (SD) Liver Test Results by Study Group and Period in Subjects Given 4, 6, or 8 Grams per Day [18]

Parameter (reference range)	Baseline	Period 2, day 7	Period 3, day 7
Placebo (n =12)			
AST (10–42 U/L)	21 (2.7)	20 (1.9)	21 (2.5)
ALT (10–60 U/L)	17 (7.9)	16 (5.1)	17 (6.0)
Bilirubin (3.4–17.1 mg/dL)	12.7 (2.5)	11.6 (2.3)	10.5 (2.4)
(58–292 _mol/L)	217 (43)	198 (39)	180 (41)
Alkaline phosphatase (42–121 U/L)	55 (13.3)	52 (11.4)	53 (11.4)
GGT (7–64 U/L)	14 (5.9)	11 (4.7)	10 (3.4)
Group I Acetaminophen (n=12)			
		4 g/day	6 g/day
AST (10–42 U/L)	22 (3.5)	23 (3.9)	24 (4.2)
ALT (10–60 U/L)	19 (8.1)	22 (8.4)	24 (7.1)
Bilirubin (3.4–17.1 mg/dL)	12.3 (3.0)	10.0 (2.0)	8.7 (1.9)
(58–292 _mol/L)	210 (51)	171 (34)	149 (32)
Alkaline phosphatase (42–121 U/L)	59 (13.0)	57 (9.8)	58 (9.7)
GGT (7–64 U/L)	15 (7.6)	12 (6.6)	14 (6.3)
Group II Acetaminophen (n = 12)			
		4 g/day	8 g/day
AST (10–42 U/L)	20 (2.2)	22 (3.0)	25 (6.4)
ALT (10–60 U/L)	17 (4.7)	20 (7.8)	26 (15.6)
Bilirubin (3.4–17.1 mg/dL)	11.8 (3.7)	11.3 (3.2)	10.4 (3.4)
(58–292 _mol/L)	202 (63)	193 (55)	178 (58)
Alkaline phosphatase (42–121 U/L)	54 (11.2)	52 (11.4)	50 (12.6)
GGT (7–64 U/L)	12 (6.2)	13 (6.4)	15 (10.9)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.			

aminotransferase determinations demonstrated no clinically important elevations at 1, 1.5, or 2 times the maximum recommended acetaminophen dose [18].

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 United States (US) [19] and the second from the United Kingdom (UK) [20].

The US prospective case series, 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 [19]. In this study, 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.

The results 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 hours) 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 hours) 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 hours) for a median duration of 72 hours.

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 [19]. This prospective, observational case series of repeated supratherapeutic overdoses indicates that the threshold for toxicity is a repeated supratherapeutic ingestion of at least 10 g/day for at least two to three days.

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 [20]. 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.

3.5.4 Repeated Supratherapeutic Overdose in Pediatric Patients

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. According to experts in medical toxicology, approximately 150 mg/kg/day for two days or more is the threshold dose needed to produce toxicity in children, although higher dosages are almost always required [2].

McNeil is particularly concerned about specific efforts to minimize the risk of cases of repeated supratherapeutic overdose in children. From as early as 1995, McNeil has urged that FDA allow the dosing instructions for children under two years of age to be added to product labels. Following a 1997 vote by the Nonprescription Drug Advisory Committee (NDAC) to support putting dosing instructions for children under two years of age on the label and subsequent discussions with FDA, McNeil submitted a Citizen's Petition in 1999 with an amendment in 2001 with further information requested by FDA [21]. In the petition, McNeil requests that FDA expand the OTC labeling of pediatric acetaminophen products to include dosing instructions for children under two years of age. As of this date, some 10 years after the NDAC vote, no final action has been taken!

3.6 Pharmacodynamics of Toxicity

The pharmacodynamics of acetaminophen overdose supports the clinical findings in regard to the threshold for toxicity. The toxicity profile of acetaminophen in acute overdoses has been well characterized [1]. Neither the parent compound nor the major metabolites (glucuronide and sulfate) are potentially toxic. Acetaminophen undergoes mixed-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 [22,23]. It is also a substrate for two sulfotransferases, SULT1A1 and SULT1A3 [24,25]. 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 [26].

About 5% to 10% of an acetaminophen dose is oxidized by cytochrome P4502E1 (CYP2E1) to produce NAPQI [27], 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 [28].

Clinical evidence demonstrates that the hepatic glucuronidation capacity for metabolizing acetaminophen is not saturated, even among those individuals who have taken considerable overdoses. Of course if hepatic dysfunction is observed, hepatic metabolism, including glucuronidation, is slowed, but glucuronidation is not saturated [29,30] in the Michaelis-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) [31,32]. However, sulfate conjugation is capacity-limited at higher doses as evidenced by a decrease in the fractional urinary excretion of sulfate metabolites [33]. 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 $\mu\text{mol}/\text{min}$ in humans, corresponding to approximately 14 g per day [14,15,13]. Therefore, the rate of consumption must substantially exceed this rate of production for an appreciable period to cause enough depletion of glutathione to allow for

cellular binding and necrosis to occur from free NAPQI. NAC replenishes glutathione and protects against necrotic cell death if administered early enough in the sequence of events [1,2].

3.6.1 Metabolic Estimation of the Acute Hepatotoxic Dose of Acetaminophen

The accepted 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 mice and hamster acute dose data [34]. In a study of adults, the amount of glutathione conjugates formed with 900, 1200, and 1800 mg doses of radiolabeled acetaminophen was 4%, and Mitchell et al [35] used these data to estimate the threshold dose for hepatic toxicity following an acute overdose. Assuming the same 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 NAPQI⁴ is 15 g taken all at once as an acute overdose: (4 mmol)(acetaminophen 151.2 mg/mmol) / 4%.

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 [34]. Hepatic production of glutathione in humans is estimated at approximately 1.62 mmol/h for a liver weight of 1500 g [14,15,13]. 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 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).

⁴Mitchell et al [35] 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 [1], 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.

These theoretical estimates are comparable to those estimated by Prescott [29] from overdose 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.

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4 CRITIQUE AND FURTHER ANALYSIS OF DATABASES CITED IN THE PROPOSED RULE

This section provides the following:

- A summary of available estimates of the incidence of acute liver failure (ALF) in the US, including data from the literature, a health insurance claims database, and the United Network for Organ Sharing (UNOS).
- A review of data summarized by FDA including case reports/series and national databases including emergency room visits based on the National Hospital Ambulatory Care Survey and 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 Toxic Exposure Surveillance System, and adverse event data from the FDA's Adverse Event Reporting System.
- McNeil's additional review of these databases, including discussion of their limitations and, when possible, updated information since the time of the FDA analysis.
- A discussion of areas of consideration for future monitoring of the effect of any labeling changes.

4.1 FDA Comments from the Proposed Rule

The following comments are from Section V, FDA's Tentative Conclusions, in the proposed rule [71 FR 377314 at 77331]:

"FDA plans to act on several fronts:

- Propose revised OTC labeling for these products
- Continue a consumer and health provider educational campaign
- Continue to monitor AERS in various databases
- Examine available data to determine whether other measures may be needed in the future to try to decrease morbidity associated with OTC acetaminophen and NSAIDs."

"FDA plans to increase its monitoring of AERS in various databases to see how this new proposed labeling, if implemented, is working to reduce injuries resulting from OTC acetaminophen and NSAID drug products and to determine whether further measures need to be proposed."

“FDA tentatively concludes that additional new labeling is needed for OTC drug products that contain acetaminophen. Data from Dr. Lee, a case series from the University of Pennsylvania Hospital, and the FDA AERS database show that unintentional overdose of acetaminophen is associated with severe hepatic injury.”

“FDA does not know the exact number of cases of liver failure or deaths related to unintentional acetaminophen overdose.”

4.2 McNeil’s Position

McNeil disagrees with some of FDA’s conclusions drawn from assessment of the case series and databases cited in the proposed rule. It is inappropriate for FDA to use case reports, case series and national databases to support proposed labeling recommendations that suggest that there is a risk of hepatotoxicity when taking therapeutic doses of acetaminophen (≤ 4 g/day). None of the presently available databases or monitoring systems are adequate to answer questions about dose, intentionality, causality, or the nature of trends in cases of serious adverse events with OTC and prescription products. Overall, more recent analyses performed by McNeil using updated information from databases reviewed by FDA indicate that cases of acetaminophen overdose, acetaminophen-associated hepatotoxicity, and acetaminophen-associated death, whether intentional or unintentional, are not increasing. McNeil strongly urges FDA, in collaboration with other stakeholders, to identify new ways to evaluate the risk of such serious events.

4.3 Key Points Supported by Scientific and Medical Data

- New analyses conducted by McNeil reveal that:
 - Hospitalization rates for ALF in the US from 1999 through 2006 have been fairly stable with rates ranging from 4.4 to 13.4 cases per million person-years, with an overall estimated rate of 10.3 per million person-years.
 - According to UNOS, drug-related ALF accounts for a very small percentage (0.5% to 1.3%) of all primary liver transplants.

- The case series (data from Dr. Lee and the Acute Liver Failure Study Group (ALFSG)) and databases that FDA cites as support for proposed labeling recommendations have serious methodological weaknesses. In nearly all instances, 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. Causality cannot be determined from these data, which do not contain a control group and likely contain biases including referral and ascertainment bias. McNeil's interpretation of Dr. Lee's data is limited particularly by the lack of access to the actual case report data.

- None of the databases provide a valid estimate of the incidence of hepatotoxicity or ALF following acetaminophen ingestion at any specified dose or with respect to what the patient's intent may or may not have been at the time of the ingestion.
- None of the databases provide a valid estimate of how outcomes with any specified dose of acetaminophen may or may not be different with respect to any specific subset of patients such as alcohol users or patients with preexisting liver disease.
- More recent analyses performed by McNeil using updated information from databases reviewed by FDA indicate that cases of acetaminophen overdose, acetaminophen-associated hepatotoxicity, and acetaminophen-associated death, whether intentional or unintentional, are not increasing.
 - The number of acetaminophen-related emergency room visits decreased from 2000 through 2004 compared with 1993 through 1999 (NHAMCS).
 - The number of deaths (458) FDA cites as being at least in part attributed to acetaminophen is an overestimate. Only 12% of these cases were reported to have ALF and at least a third had another drug listed as an underlying cause of death (MCOB).
 - In the years since 1999 when ICD-10 codes were initiated, the rate of age-adjusted ALF mortality and acetaminophen-associated ALF mortality, have not shown an increasing trend (MCOB).
 - Most calls to poison centers for acetaminophen are for acute accidental ingestion in children and are related to exploratory ingestions or exposures. Since 2002, for adults and children older than 12 years of age, most calls to poison centers for acetaminophen were reported as intentional ingestion; unintentional acetaminophen ingestion represented a small proportion of calls for this age group and has not increased over time (TESS).
 - A stable pattern of reporting was observed for hepatic events involving OTC acetaminophen products as a suspect drug in non-suicide cases during the years 2004 through 2006 (AERS).

- New systems and databases should be designed to have the sensitivity to reliably measure the impact, if any, of the changes to a products label and educational initiatives.
 - Since such a high percentage of consumers report using acetaminophen-containing products according to the label instructions, it is unlikely that the databases that FDA has historically used have the ability to detect meaningful changes, even when they occur, in consumer behavior. In addition, changes in consumer behavior may not immediately translate into an observable decrease in the number of cases of hepatotoxicity.
 - New systems should be designed to obtain reliable information on targeted events, eg, unintentional overdose.

4.4 Estimates of the Incidence of ALF

It is important to have reliable estimates of the incidence of ALF. True changes in the occurrence of acetaminophen-associated ALF would also be associated with changes in the overall incidence of ALF. There are no comprehensive registries or population-based surveillance programs to determine the incidence of ALF. Using liver transplantation programs, single hospital or county case reports, and national databases, the incidence of ALF in the US is estimated to be approximately 1000 to 2800 cases per year [1, 2 and 71FR 377314 at 77317].

4.4.1 McNeil's Database Analyses

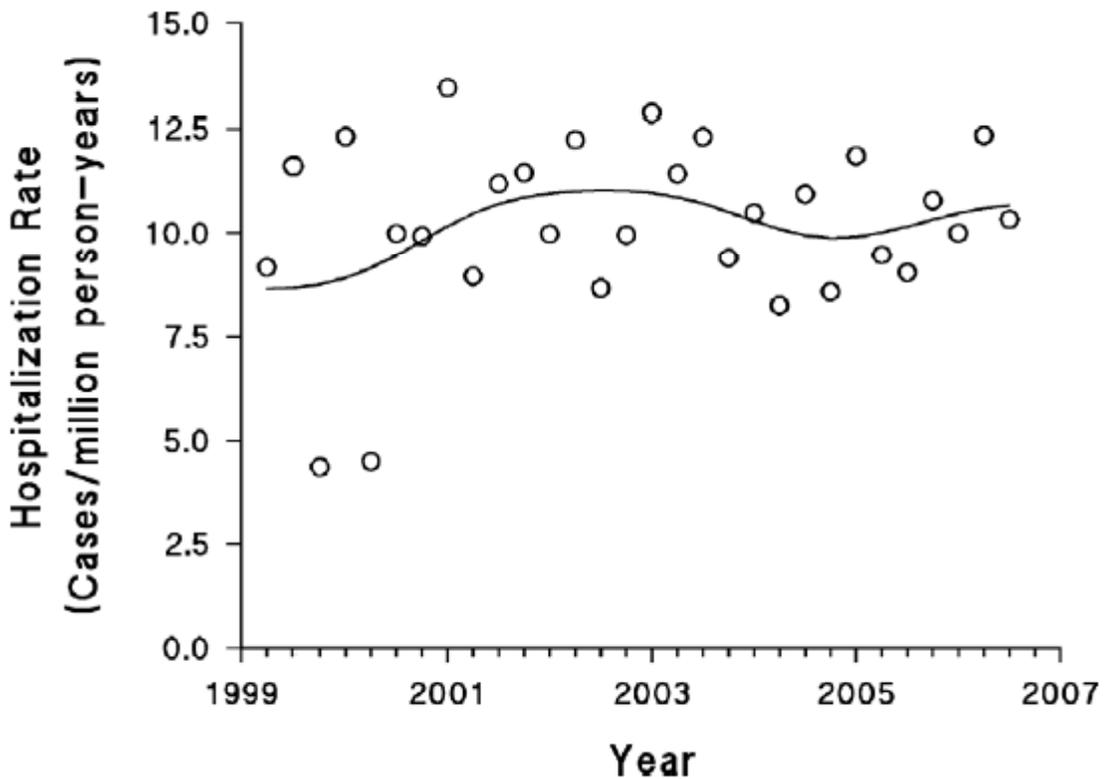
Since reliable estimates of incidence of ALF overall and over time are not available, McNeil commissioned an analysis to estimate the incidence of hospitalization for ALF in a defined US population by calendar year. A large health care insurance database, PharMetrics Patient-Centric database that reflects the health care utilization of 55 million people in more than 80 health plans in the US, was accessed. This analysis showed that hospitalization for ALF is not increasing.

Health insurance claims data for the years 1999 through June 2006 were reviewed. Data included pharmacy outpatient prescription dispensings, inpatient and outpatient provider and facility claims (with diagnoses in ICD-9 codes and procedures in ICD-9 and CPT codes) and the overall number of insured by age, gender and calendar year. This information was used to identify first hospitalizations with a primary discharge diagnosis of acute/subacute necrosis of the liver (ICD-9 code 570), and to obtain demographic and other

cofactor information related to the hospitalization. Using the denominator data of all individuals served by the health plans database, the incidence of ALF over time was estimated. Five-year age groups for each combination of year, calendar quarter, and sex were created. Rates were standardized for each calendar quarter by age and sex, weighting the rates to remove the effect of any variations in age and sex distribution over time. Rates were standardized to the age and sex distribution of the whole database. Observed and smoothed standardized incidence rates were graphed by calendar quarter, using a Savitzky-Golay smoothing algorithm.

Figure 1 shows the hospitalization rates of ALF by year from 1999 through 2006 expressed as cases per million person-years standardized for age and sex. These data show a fairly stable pattern with rates ranging from 4.4 to 13.4 cases per million person-years. Smoothed rates, indicated by the line, indicate hospitalization rates between 9 and 11 cases per million person-years, with an overall estimated rate of 10.3 per million person-years. The lack of a clear rise or fall in rates over recent years indicates that hospitalization for ALF has been stable during this time period.

Figure 1. Hospitalization Rates for Acute Liver Failure by Calendar Year and Quarter, Expressed as Cases per Million Person-years and Standardized for Age and Sex



Data were obtained from the United Network for Organ Sharing (UNOS) website for the time period 1988 through 2006 [3]. As shown in Table 1, these data indicate that the percentage of primary liver transplants in adults (> 18 years) with a reported primary diagnosis of drug-related acute hepatic necrosis is not increasing and has been consistently low (0.5% to 1.3%). It should be noted that participation in UNOS has increased over time, and participation rates could have influenced the number of transplants reported by year. The number of Medicare approved adult liver transplant centers has also increased from 66 in 1998 to 89 in 2005 [4].

Table 1. Organ Procurement and Transplantation Network – Number and Percent of Adult Primary Liver Transplants With a Reported Primary Diagnosis of Drug-Related Acute Hepatic Necrosis, 1988 Through 2006

Year	Adult Primary Liver Transplants N	Drug-Related Acute Hepatic Necrosis N	Drug – Related Acute Hepatic Necrosis %
1988	992	13	1.3
1989	1299	15	1.2
1990	1719	10	0.6
1991	2062	10	0.5
1992	2130	23	1.1
1993	2455	33	1.3
1994	2744	24	0.9
1995	3071	24	0.8
1996	3149	29	0.9
1997	3194	28	0.9
1998	3556	28	0.8
1999	3818	32	0.8
2000	4008	35	0.9
2001	4195	38	0.9
2002	4384	32	0.7
2003	4726	39	0.8
2004	5165	43	0.8
2005	5385	48	0.9
2006	5591	54	1.0

Table 2 provides UNOS data that further confirm that ALF that may be secondary to acetaminophen overdose remains a relatively small proportion of all ALF cases (21%) that are transplanted or are waiting for a transplant. ALF that may be attributed to acetaminophen was reported in 61% of drug-related ALF cases.

Table 2. Organ Procurement and Transplant Network - Wait-listed and Transplanted Adult (Age 13 and Older) Liver Patients by Year and Diagnosis

Year	Liver Transplants/ Waitlistings N	AHN n (%)	Drug-related AHN n (% of AHN)	Acetaminophen -related AHN, n (% of Drug- related AHN)	Acetaminophen- related AHN, n (% of AHN)
1998	8294	311 (3.7)	110 (35.4)	59 (53.6)	59 (19.0)
1999	9359	440 (4.7)	129 (29.3)	79 (61.2)	79 (18.0)
2000	9708	402 (4.1)	121 (30.1)	71 (58.7)	71 (17.7)
2001	9737	422 (4.3)	111 (26.3)	67 (60.4)	67 (15.9)
2002	8948	398 (4.4)	146 (36.7)	87 (59.6)	87 (21.9)
2003	9469	339 (3.6)	136 (40.1)	78 (57.4)	78 (23.0)
2004	10183	414 (4.1)	159 (38.4)	108 (67.9)	108 (26.1)
2005	10828	478 (4.4)	174 (36.4)	110 (63.2)	110 (23.0)
Total	76526	3204 (4.2)	1086 (33.9)	659 (60.7)	659 (20.6)
Mean	9566	401	136	82	82

Abbreviations: AHN = acute hepatic necrosis

It is important to note that while estimates of the proportion of transplanted or waitlisted ALF cases that are considered to be drug-related and more specifically acetaminophen-related can be made, as is the case for case reports and case series, the assignment of relatedness is based on physician judgment that may or may not be based upon confirmatory data. Dosing information is not available, so this data source cannot address therapeutic use versus overdose. Additionally, no control data are available.

4.4.2 Summary

The incidence of ALF has been estimated as 1000 to 2800 cases per year in the US. Hospitalization rates for ALF in the US from 1999 to 2006 have been fairly stable with rates ranging from 4.4 to 13.4 cases per million person-years, with an overall estimated rate of 10.3 per million person-years. Drug-related ALF is rare and has been reported for 0.5 to 1.3% of all primary liver transplants based on UNOS data. ALF that may be attributed to acetaminophen was reported in 21% of all ALF cases and 61% of drug-related ALF cases of liver transplants or waitlistings for transplants from 1998 to 2005.

4.5 Review of Data Summarized by FDA

4.5.1 Limitations of Case Reports and Case Series Described by FDA

FDA has based its decision on the need for labeling changes for acetaminophen at least in part on case reports and case series presentations at the 2002 NDAC meeting, including Dr. Lee's case series, and other case series in the scientific literature. Published reports from Acute Liver Failure Study Group (ALFSG) members have updated the findings presented by Dr. Lee.

Results from these case reports and case series are inherently of limited value and provide no reliable evidence of acetaminophen toxicity at the maximum-labeled daily doses of acetaminophen.

These case series suffer from recall bias as well as referral bias. Information on acetaminophen dose and intentionality are often inaccurate because of problems with recall and social stigma associated with admission of suicide attempts. Individuals tend to under-report medication history even with their best cognition [5]. Furthermore, suicide as a reason for overdose is also likely under-reported. Disclosure of suicidal intent may be of concern given possible repercussions (eg, loss of insurance coverage, privacy, social stigma, and family impact). Given these disclosure issues, classification of intent of ingestion as unintentional cannot be done with certainty.

Case reports and even relatively large case series, such as the ALFSG's case series, are not useful for assessing causality of an exposure-disease relationship [6]. Such reports simply describe the concurrence of an exposure and a disease in an individual or series of individuals, but do not provide rates of disease among the exposed, and do not provide information on whether the rate of occurrence of the disease is greater among the exposed than among a comparable unexposed population. In the case series reported, no historical or concurrent controls have been provided to estimate the extent of acetaminophen use in the general population covered by the reports or case series. Without a control group, one cannot determine whether exposure reported in the cases exceeds that in a group of controls, and thus one cannot infer causality of acetaminophen use in cases and liver toxicity. In addition, these case series often lack clinical measurements or pathological findings that could link acetaminophen exposure to liver toxicity.

If the exposure and the disease are both rare, then case reports can provide a signal for further investigation into a possible causal relationship. When the exposure is common, as

in the case for acetaminophen, observational epidemiological studies (primarily case-control and cohort studies) are needed to provide quantitative estimates of the rates of disease among those exposed compared to unexposed. However, no systematic analytic epidemiologic studies were found reporting the relative risk of ALF or mortality according to the acetaminophen dose ingested, either intentionally or unintentionally.

The existing scientific literature consistently shows that the number of ALF cases and deaths in the US associated with acetaminophen use are low. Most of these serious adverse events are reported to be associated with attempted suicide, but the literature is less consistent with regard to the percentage reported to be related to unintentional acetaminophen overdose.

4.5.1.1 *Acute Liver Failure Study Group (ALFSG) Case Series*

Ostapowicz [7] reported ALFSG data for 308 consecutive patients with ALF over a 41-month period during 1998 to 2001 admitted to 17 tertiary care liver centers in the US. Some of these data were presented by Dr. Lee at the 2002 NDAC meeting. Acetaminophen ingestion was reported to be associated with 120 ALF cases (39%). After the 2002 NDA meeting, Larson [8] extended the Ostapowicz report describing 662 consecutive ALF patients at 22 tertiary care centers during the period 1998 to 2003. Among these patients, 275 (42%) were considered to be associated with acetaminophen.

In Larson's case series [8], ALF was attributed to acetaminophen exposure if one of the following three criteria was satisfied: (1) history (self-report or family member report) of ingestion of > 4 g/day acetaminophen within seven days of presentation; (2) detection of any level of acetaminophen in serum; or (3) a serum alanine aminotransferase level exceeding 1000 IU/L with a history of acetaminophen ingestion. Information on acetaminophen use and alcohol consumption was obtained from a "careful history" taken "where possible for each patient."

In an attempt to better understand the ALFSG data, McNeil has repeatedly asked for access to redacted source data. Since repeated requests have been denied, McNeil is only able to comment on what has been published.

- A percentage of the general population without ALF would meet each of the criteria that were used to attribute acetaminophen exposure to ALF.
 - Attributing a case to acetaminophen based on any one of these criteria alone could falsely attribute ALF to acetaminophen. Given the common nature of

acetaminophen exposure, it is unreasonable to assume that the simultaneous presence of that common exposure and ALF, makes the two events related.

- The inclusion criterion of any detectable serum acetaminophen as acetaminophen-related ALF likely artificially inflated the number of acetaminophen-associated cases. Since exclusion criteria did not specifically exclude conditions such as hepatitis C, hepatotoxic drug exposure, or viral etiologies, individuals with undiagnosed acute hepatitis who may have taken therapeutic doses of acetaminophen would have been assigned to the unintentional overdose group. It was noted that 13% of the cases were classified as acetaminophen-related by meeting only one of the three diagnostic criteria, but it was not reported how many met only the serum acetaminophen criterion [8]. Selection bias is probable [9].
- The acetaminophen doses reported as ingested are likely not the true doses ingested. Significant recall bias has affected the reporting of dose. Additionally, true intent at the time of acetaminophen ingestion cannot be determined.
 - Of the 275 acetaminophen-associated ALF cases, 122 (44%) were classified as intentional overdose, 131 (48%) were classified as unintentional acetaminophen overdose, and intent was unknown in 22 cases (8%) [8].
 - Doses of 4 g/day or less were reported by 19 patients; five of these cases were classified as intentional overdose, with one suicide reportedly attempted by ingestion of 1.2 g of acetaminophen [8]. Cumulative doses as low as 2.5 g and daily doses as low as 1 g/day were reported for the unintentional overdose group [8]. The highest estimates of unintentional overdose and ALF alleged to be related to doses of acetaminophen ≤ 4 g/day are reported by the ALFSG. Converting their reported percentage figures into rates, upper bounds of three deaths per year per million acetaminophen users would be associated with unintentional overdose and less than one death per year per million would be associated with therapeutic doses. Yet these estimates are two or more times higher than estimates based on FDA or British data. It is important to note that given the widespread usage of acetaminophen products, if there were any substantial increased risk of ALF or mortality due to unintentional acetaminophen poisoning, the numbers of observed cases of ALF and deaths from acetaminophen overdose would have been far greater than those actually observed.

- Altered cognition due to encephalopathy, casts considerable doubt on both estimates of dose and the classification of intent of acetaminophen exposure.
- Use of prescription narcotic-acetaminophen products was reported.
 - Fifteen percent (15%) of cases reportedly used an narcotic-acetaminophen prescription product and an OTC acetaminophen product at the same time [8].
 - Use of a prescription narcotic-acetaminophen combination product was reported more frequently for unintentional acetaminophen overdose cases (63%) than for intentional acetaminophen overdose cases (18%) [8].
- Since 2002, the percentage of ALF cases attributed to acetaminophen in this case series has remained stable.
 - Larson reported that the percentage of ALF cases associated with acetaminophen increased from 28% in 1998 to 51% in 2003 [8]. In 2006, Dr. Lee presented slightly different percentages for the same years, 32% in 1998 and 50% in 2003 [10]. Dr. Lee also presented percentages for 2002, 2004, and 2005 (only partial data presented for 2005), of 49%, 52%, and 42%.

4.5.1.2 *Other Case Series Reported in the Scientific Literature Cited by FDA*

In the Proposed Rule [71 FR 377314 at 77319-20], FDA provides data from five case series that reported information on intentionality and the number of unintentional cases using therapeutic doses of acetaminophen, ie, ≤ 4 g/day. These cases series were from a review of the published literature that included series with ten or more cases published within the ten years preceding the 2002 NDAC meeting. It should be noted that standard methodologies used for data collection [11] such as (1) explicit protocols for case selection and exclusion, (2) abstractor training, (3) clear predetermined definitions of important variables (how dose and duration of acetaminophen and alcohol is to be determined or specific definitions for “intentional” and “unintentional” classification), (4) blinding of chart reviewers to the hypotheses being tested and group assignments, (5) assessment of interrater reliability and use of standardized abstraction, and (6) coding forms designed to promote more uniform handling of data, especially data that are conflicting, are not fully reported for these case series.

Johnston [12] reported on purported unintentional acetaminophen toxicity in alcoholic patients and presented two case reports followed by a review of an additional 51 cases of hepatotoxicity in alcoholics from the literature for the period 1966 to 1995. Review of case listings indicated that 12 of the 53 cases reported taking ≤ 4 g/day of acetaminophen. The authors acknowledged, "The amount of acetaminophen or alcohol ingested by patients may be subject to recall bias, withholding of information by the patient, or nonresponsive state of the patient upon presentation." Comparisons of the reported amounts of acetaminophen consumed with measured levels of acetaminophen provided direct evidence of the unreliability of the reported doses. For example, a patient who reported use of 6 g acetaminophen in a single day for headache relief had a plasma acetaminophen level of 237 $\mu\text{g}/\text{mL}$ 17 hours after admission for treatment. This plasma level is inconsistent with the reported dose ingested.

Schioldt [13] reviewed medical records for cases hospitalized for "excessive acetaminophen ingestion" at a Dallas hospital from 1992 to 1995. Fifty (50) cases were classified as suicide attempts and 21 as accidental poisonings. Five of the 71 cases had reported ingesting no more than a therapeutic dose of acetaminophen. Two of the five were said to have attempted suicide, which would make a therapeutic dose of acetaminophen unlikely. The remaining three were considered to be unintentional cases, and it was reported that unintentional cases had frequent evidence of alcohol abuse; dosing estimates from alcoholics are known to be unreliable.

In 1995, Zimmerman [14] reported findings in 67 of 81 reports of alcoholics who had hepatotoxicity associated with unintentional acetaminophen overdose. Cases were not systemically obtained but rather were reported by hepatologists or other colleagues who became aware of this industry-sponsored registry by solicitation correspondence from the authors; thus, referral bias is clearly an issue with these data. Doses of no more than 4 g/day were reported in 27 of the cases. However, the authors stated that, "adequate data on amounts of alcohol, duration of intake, or interval between intake of alcohol and intake of APAP are not available." Remarkably, however, the authors fail to express any concern about the accuracy of acetaminophen dosage information, despite acknowledgement that, "almost all of the 161 patients... drank regularly and to excess..."

Whitcomb [15] reported 49 cases of acetaminophen overdose hepatotoxicity (defined as $\text{AST} > 1000 \text{ U/L}$) based on approximately 19,500 discharges per year in the University of Pittsburgh Medical Center hospitals (no estimates of the size of the population covered by the hospitals was included) during the 78-month period from January 1987 to July 1993. All

49 ALF cases exceeded the recommended daily dose; in 28 cases (57%) the dose was exceeded intentionally. For the remaining 21 patients where the overdose was said to be unintentional, ten had consumed between 4 and 10 g/day, eight had consumed > 10 g/day, and dose was unquantifiable in three patients. No case of hepatotoxicity in this series was associated with an acetaminophen dose \leq 4 g/day.

Broughan reported on a case series of 48 acetaminophen overdose patients seen between 1990 and 1996 at the University of Texas Medical Branch in Galveston that included 40 patients who attempted suicide and eight who reported accidental overdose [16]. None of the patients reported ingestion of <4 g/day of acetaminophen. The authors stated the following regarding the difficulties in evaluating intent and dosage in studies of drug overdose cases, "One should never completely accept the history in a drug overdose case. The patient is almost always alone during this situation and reconstruction of what drugs were taken, when they were taken, and how much was taken are a guess at best."

4.5.2 Databases Reviewed by FDA in the Proposed Rule: McNeil's Review, Discussion of Limitations, and Updated Analyses

FDA used several databases to estimate the occurrence of acetaminophen-associated hepatotoxicity [17]. 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 as well as a review of McNeil's additional analyses of databases.

Overall, more recent analyses performed by McNeil using updated information from the databases reviewed by FDA indicate that cases of acetaminophen overdose, acetaminophen-associated hepatotoxicity, and acetaminophen-associated death, whether intentional or unintentional are not increasing.

- The number of acetaminophen-related emergency room visits decreased from 2000 through 2004 compared with 1993 through 1999 (NHAMCS).
- The number and age-adjusted rate of hospitalizations with unintentional acetaminophen overdose represent a small proportion of all hospitalizations with acetaminophen overdose, and occur with low frequency. The rate of hospitalization with unintentional overdose did not increase during the period from 2000 to 2004 (NHDS).
- The number of deaths (458) FDA cites as being at least in part attributed to acetaminophen is an overestimate. Only 12% of these cases were reported to have ALF and at least a third had another drug listed as an underlying cause of death (MCOD).
- In the years since 1999 when ICD-10 codes were initiated, the rate of age-adjusted ALF mortality and acetaminophen-associated ALF mortality, have not shown an increasing trend (MCOD).
- Most calls to poison centers for acetaminophen are for acute accidental ingestion in children and are related to exploratory ingestions or exposures. Since 2002, for adults and children older than 12 years of age, most calls to poison centers for acetaminophen were reported as intentional ingestion; unintentional acetaminophen ingestion represented a small proportion of calls for this age group and has not increased over time (TESS).
- A stable pattern of reporting was observed for hepatic events involving OTC acetaminophen products as a suspect drug in non-suicide cases during the years 2004 through 2006 (AERS).

4.5.2.1 The National Hospital Ambulatory Care Survey (NHAMCS): Emergency Department Component

The NHAMCS is conducted on an annual basis by the Centers for Disease Control and Prevention, National Center for Health Statistics. A survey of ambulatory care services in hospital emergency departments (EDs) is one of the components of NHAMCS. FDA's review by Nourjah [17] compiled information pertaining to any visits with ICD-9 codes for acetaminophen poisoning (965.4 or E850.4) during the period 1993 through 1999, and reported that acetaminophen overdose was associated with an annual average of 56,000 ED visits during the six-year time period.

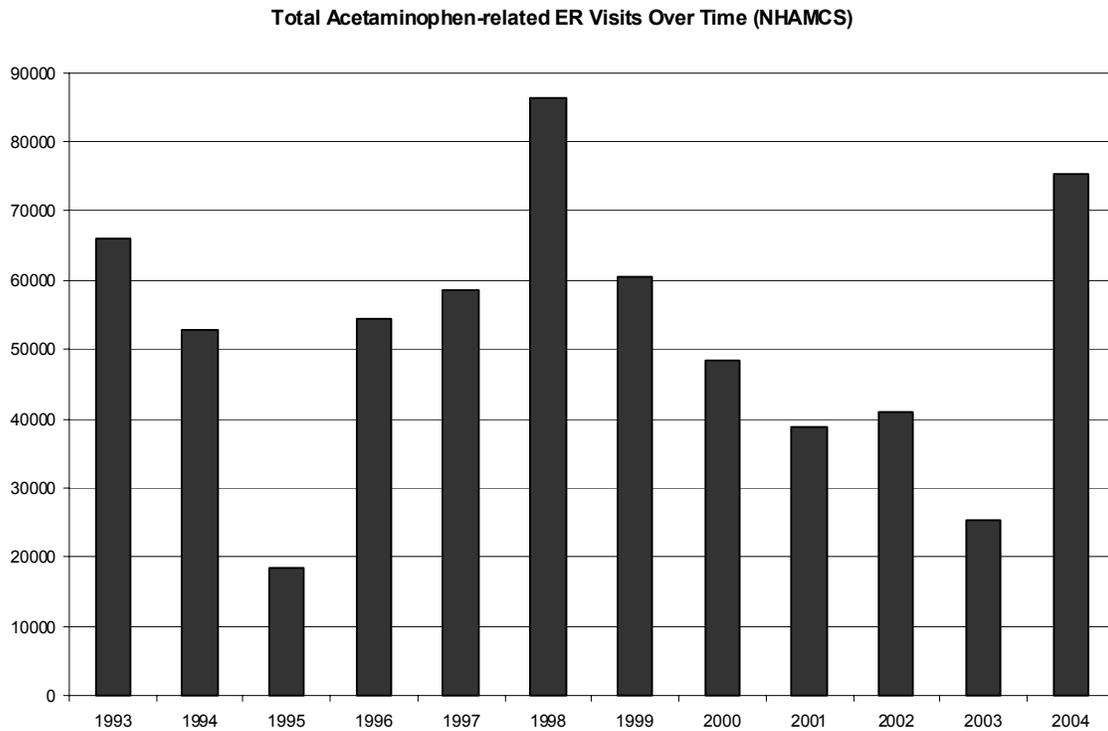
4.5.2.1.1 McNeil's Review and Limitations of Data - NHAMCS

Reports included pediatric visits, and were based on a sampling of 600 participatory hospitals that changed over time. The hospitals included in the survey vary from year to year. Changes in the sampling design and the survey instrument (the patient record) have changed over time, which may have contributed to changes in number of visits per year. Given the variability, it is reasonable to look at groups of years, instead of individual years. Intentionality is not assessed by NHAMCS, and the accuracy of the diagnosis reported by the participating EDs is not confirmed.

4.5.2.1.2 *McNeil's Updated Analysis 2000 Through 2004 - NHAMCS*

Figure 2 shows an extension of the data presented by FDA. As done in FDA's analysis, ICD-9 codes 965.4 or E850.4 were used to identify acetaminophen-associated cases. As shown in Figure 2, during the period from 2000 to 2004 there was an average of 45,734 ED visits per year. These data suggest that the number of acetaminophen-associated emergency department visits has decreased during the period 2000 through 2004 (45,734 per year) compared to the period presented by FDA, ie, 1993 through 1999 (56,000 per year).

Figure 2



4.5.2.2 *National Electronic Injury Surveillance System (NEISS)*

The NEISS collects information on consumer product-related injuries treated in EDs of 100 hospitals selected as a probability sample of the over 5000 US hospitals with EDs [18]. 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 [18]. FDA's review by Nourjah 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 [17]. Based on data from 2001, FDA estimated that 23% of acetaminophen-associated overdoses that led to ED visits were unintentional, 56% were intentional, and 20% were of unknown intent.

4.5.2.2.1 *McNeil's Review and Limitations of Data - NEISS*

The FDA's analysis was conducted using specific CD-ROM files made available solely to federal government agencies; these files contain hospital identifiers and product names that are not releasable to the public. In addition, the representativeness of this database is unknown, and the accuracy of intentionality based on a comment field is questionable.

Although age-specific intentionality data were not presented, it appears that a large majority of the ED visits associated with unintentional acetaminophen overdose occurred in children. For example, Table 2 in the Nourjah paper indicated that 17% of ED visits identified by NEISS for acetaminophen-associated overdoses were in children less than six years of age [17]. 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. 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. 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 exploratory ingestions.

4.5.2.2.2 *McNeil's Updated Analysis - NEISS*

As noted above, McNeil was unable to obtain the source data to update the FDA's analysis.

4.5.2.3 *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 [17]. Nourjah reported that 74% of hospitalizations with acetaminophen overdose were categorized as intentional, 8% as accidental, and 17% as unknown intention. Event rates using population estimates and trends over time were not reported by FDA.

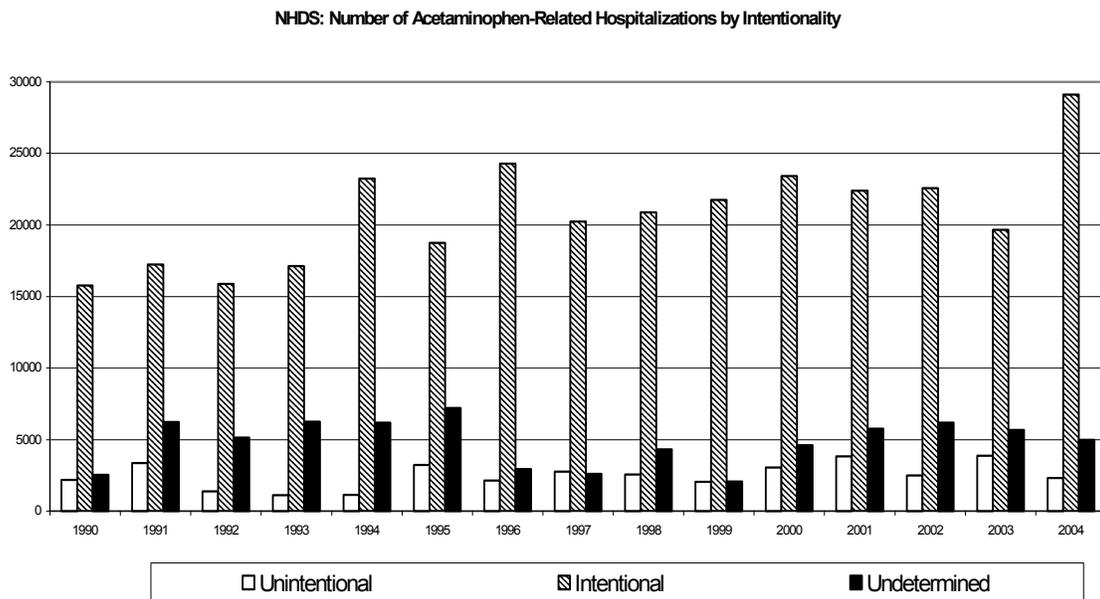
4.5.2.3.1 *McNeil's Review and Limitations of Data - NHDS*

This database includes a large number of pediatric hospitalizations, as well as readmissions for the same diagnosis. Although age-specific intentionality data were not presented, it appears that many of the hospitalizations associated with unintentional acetaminophen overdose occurred in children. Table 2 in the Nourjah paper indicated that 2% of hospitalizations occurred in children less than six years of age and 22% in children age six to 16 years of age [17]. Since only 8% of the hospitalizations were said to be associated with unintentional overdoses, it appears that the majority of hospitalizations for unintentional acetaminophen overdoses were for children. Use of the data as reported by Nourjah to evaluate unintentional acetaminophen overdose in adults is misleading, since this analysis included accidental overdoses in young children.

4.5.2.3.2 *McNeil's Updated Analysis for the Time Period 2000 to 2004 - NHDS*

Figure 3 shows an extension of the NHDS data summarized by FDA. The FDA's analysis included data through 1999. Data are presented by intentionality, as previously defined by FDA, with categories of intentional, unintentional, and undetermined (unknown/other). McNeil's updated analysis shows that during the period 2000 to 2004, approximately 31,900 acetaminophen-associated hospitalizations were estimated to occur per year. As was true for the FDA analysis, these data included pediatric cases. Hospitalizations with unintentional acetaminophen overdose represent a small proportion of all hospitalizations with acetaminophen overdose, and occur with low frequency. The number of hospitalizations with unintentional overdose did not increase during from 2000 to 2004.

Figure 3



McNeil has also calculated age-adjusted rates of acetaminophen-associated hospitalizations from the NHDS database. Supplemental Figure 1 in Attachment 1 shows the rate of acetaminophen-associated hospitalization expressed as the number of hospitalizations per 100,000 US population, age adjusted based on the population of base year 2000, and including a three-year moving average line which smoothes out the variation that occurs on an annual basis. Supplemental Figures 2 and 3 provide additional analyses of these data, including the age-adjusted rate of hospitalizations expressed as the number of acetaminophen-associated hospitalizations per 100,000 hospitalizations, overall and for those ten years and older. Consistent results were observed.

4.5.2.4 *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 [17]. 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 E850.2 (accidental acetaminophen poisoning). FDA estimated that an average of 458 deaths/year were at least in part attributable to acetaminophen overdose. However, event rates using population estimates and trends over time were not reported by FDA.

4.5.2.4.1 *McNeil's Review and Limitations of Data - MCOD*

Death certificate data are known to be limited by misclassification in part due to the frequently inadequate information of the decedent's medical history available to the certifying physician. In addition, distinguishing between acetaminophen overdose as a contributing or underlying cause of death is important in the evaluation of acetaminophen-related deaths. The codes are listed by the individual filling out the death certificate, and the accuracy of coding is not monitored.

In FDA's analysis, most of the potential acetaminophen-associated deaths were identified because poisoning by acetaminophen was listed as a contributing cause of death, but for many of these deaths, acetaminophen ingestion seems unlikely to have played a major role in causing death. Nearly one-third of the deaths with acetaminophen listed as a contributing cause of death indicated that the underlying cause of death was suicide by ingestion of some other specified drug, accidental poisoning from ingestion of another specified drug, or poisoning from ingestion of another drug with intent unknown.

Including only deaths at all likely to be associated with acetaminophen, ie, with (a) underlying cause listed as accidental acetaminophen poisoning, (b) underlying cause listed as suicide and acetaminophen poisoning listed as a contributing cause of death, and (c) underlying cause listed as poisoning with unknown intent and acetaminophen listed as a contributing cause of death, results in an estimated number of acetaminophen-associated deaths of 226 per year. Even this number overstates the actual number of deaths from acetaminophen poisoning, because many deaths in categories (b) and (c) had drugs or exposures listed in addition to acetaminophen as competing causes of death.

In addition, only 12% of all deaths identified in FDA's analysis as possibly being associated with acetaminophen toxicity listed ALF (ICD-9 codes 570, 572.2, 572.4, 573.8, or 573.9) as

an underlying or contributing cause of death, suggesting that acetaminophen may have played only a minor role in many of the 458 deaths identified by FDA as being potentially acetaminophen-associated. All of these factors indicate the number of deaths associated with acetaminophen overdose is substantially lower than 458 per year.

4.5.2.4.2 McNeil's Updated Analysis 1999 to 2004 - MCOB

Age-adjusted rates (per 100,000 population) for ages 10 and older from the national multiple cause of death files for the years 1999 to 2004, are presented in Figures 4 and 5. In 1999, the use of ICD-10 codes was initiated for US mortality data. An ICD-10 code of T39.1 was used to identify acetaminophen poisoning as an underlying cause of death. Liver disease ICD-10 codes were chosen by reviewing all deaths from suicide by ingestion of analgesic, antipyretic, or antirheumatic drugs in the years 1999 to 2004 that had acetaminophen-poisoning listed as a contributing cause of death, and then selecting the liver disease codes (excluding alcohol liver diseases and chronic liver diseases) that were listed two or more times. The ICD-10 liver disease codes that met these criteria were: K72.0 (acute/subacute liver failure), K72.9 (hepatic failure, unspecified), K67.7 (hepatorenal failure), K71.9 (toxic liver disease, unspecified), K75.9 (inflammatory liver disorder, unspecified) and K76.9 (liver disease, unspecified). The code K72.9 (hepatic failure, unspecified) was the single most common liver disease code listed for acetaminophen-associated suicides. Of note, there is an ICD-10 code for toxic liver disease due to drugs, ie, K71.1. This code was not found in the most commonly used liver codes for acetaminophen deaths, although it appears to be the most appropriate.

Figure 4 shows age-adjusted acetaminophen-associated ALF mortality rates for the years 1999 through 2004. Age-adjusted acetaminophen-associated ALF mortality rates were stable for the years 1999 through 2004. These data do not support the assertion that the number of acetaminophen-associated ALF deaths is increasing.

Figure 4

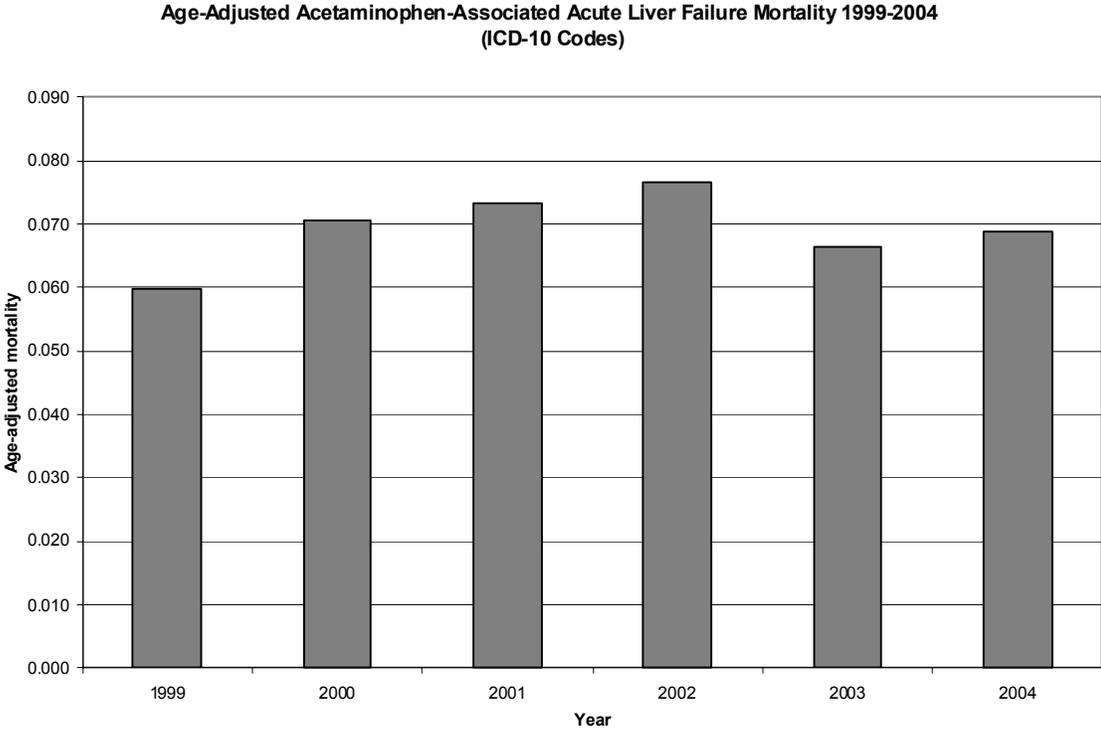
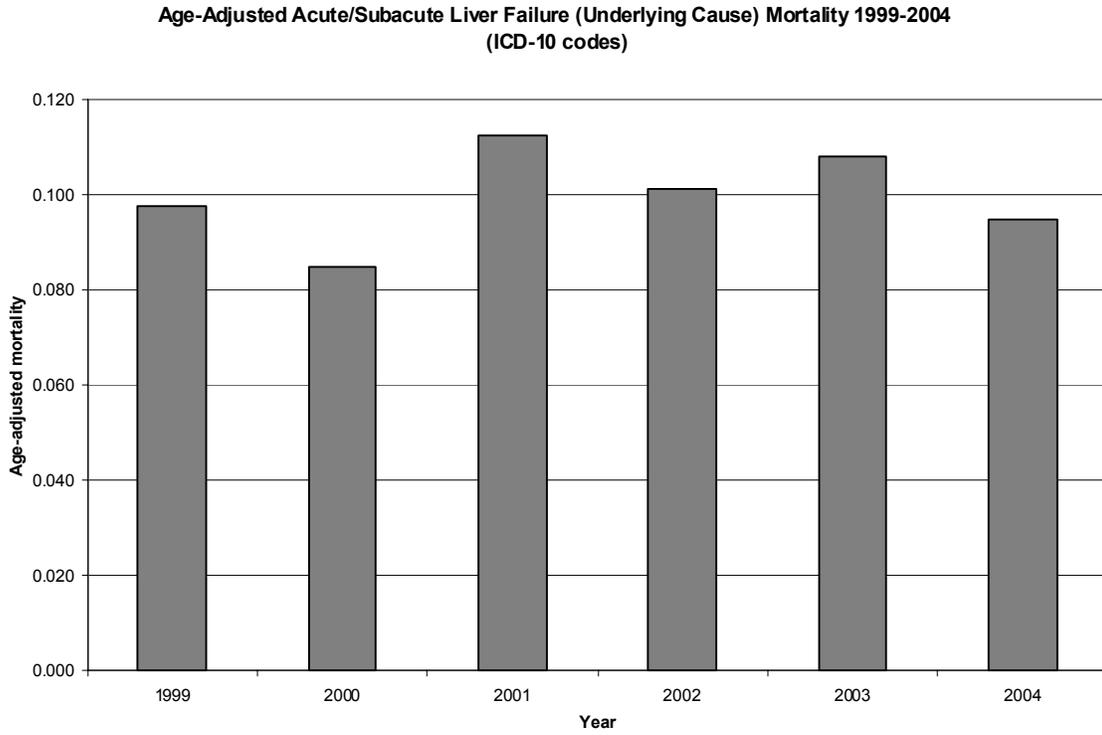


Figure 5 shows age-adjusted mortality with acute/subacute liver failure as an underlying cause for the years 1999 through 2004. No apparent trend in the rate of acute/subacute liver failure as an underlying cause of mortality was observed.

Figure 5



4.5.2.5 *Toxic Exposure Surveillance System (TESS)*

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 [17] 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. Nourjah reported that in 2001 nearly 50% of all acetaminophen exposures reported were unintentional in nature; 173 acetaminophen-associated fatalities occurred, of which 55% were reported to be intentional and 26% were unintentional.

4.5.2.5.1 *McNeil's Review and Limitations of Data - TESS*

It is important to note that the Nourjah analysis included pediatric cases. The percentage of TESS reports that are unintentional is much lower for adults, ie, 25% (see Section 4.5.2.6.2), and adult products are the focus of the current labeling discussion. It is 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, TESS 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. Such re-categorization alters the reported percentages by intentionality in comparison to the AAPCC annual reports, and is potentially misleading.

As with other post-marketing spontaneous adverse event reports, the accuracy of the information, including dose of drug, for each TESS case is dependent upon the person calling the poison control center. The caller may be the individual involved in the incident, a family member, a childcare provider, a health care professional, etc. Relatedness of clinical events to drug exposure is determined by the poison control center staff and is often based on incomplete information making it impossible to rule out all other causes. In addition, participation of poison control centers changes year-to-year, adding to the difficulty of evaluating trends over time.

4.5.2.5.2 *McNeil's Updated Analysis 2000 to 2006 - TESS*

Figures 6 through 8 provide data from the TESS from 2000 to 2006 on acetaminophen-related calls to poison centers for those greater than 12 years of age. Data are presented by year by intentionality, in categories of intentional, unintentional, and other. In these figures, rates of acetaminophen-related calls to the poison centers are presented per 100,000 population served. The total rates of acetaminophen-related calls for each year are also provided. Data were obtained from the annual reports and intentionality was summarized as provided in the reports. The category of 'intentional' included suspected suicidal, intentional misuse, intentional abuse, and intentional unknown. The category of 'unintentional' included therapeutic error, unintentional misuse, and unintentional unknown. The category of 'other' included contaminant/tampering, malicious, and withdrawal. In addition to intentional, unintentional, and other, the total category also included adverse reactions and unknown. In addition to the annual information, a three-year moving average line is provided; this smoothes out the variation that occurs on an annual basis. Figure 6 provides rates of *all* acetaminophen-related calls, and shows a slight increase in the total rate of calls per year over time, from 24.2 in 2000 to 29.4 in 2006. It is 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. Overall, 70% of calls were for intentional ingestions; unintentional ingestions accounted for 25% of calls, and were stable over time.

Figure 6

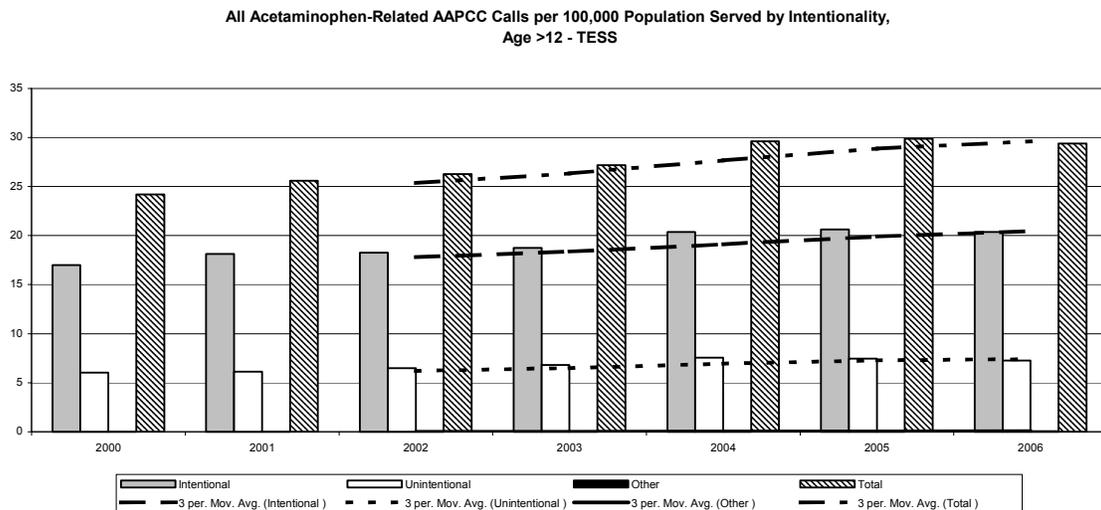


Figure 7 presents the rate of calls for *single-ingredient* acetaminophen products for 2000 to 2006 by intentionality and overall. Calls for *single-ingredient* acetaminophen products show a negligible increase in the total rate of calls per year over time, from 9.2 in 2000 to 10.1 in 2006. Overall, 71% of calls were for intentional ingestions; unintentional ingestions accounted for 27% of calls, and were stable over time.

Figure 7

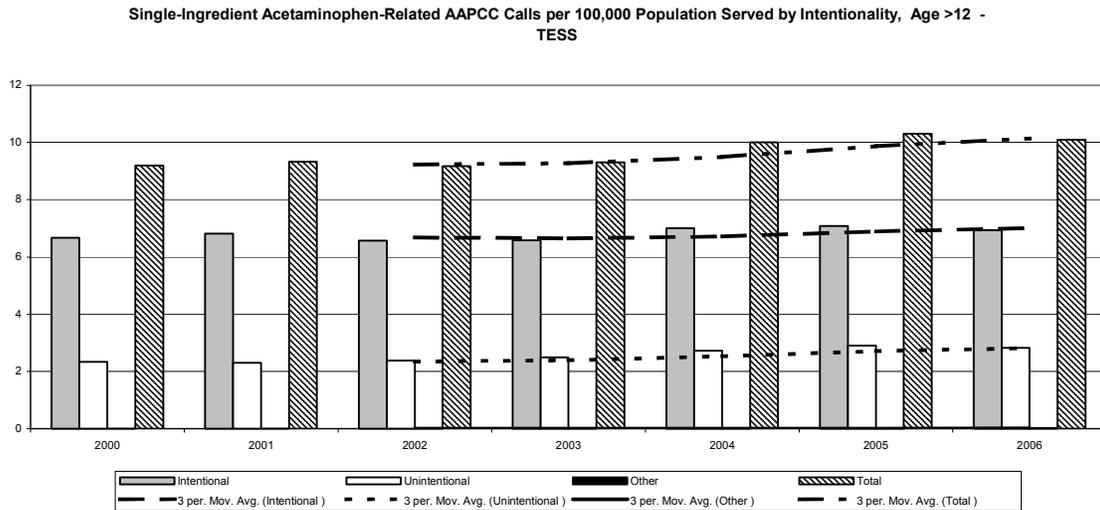
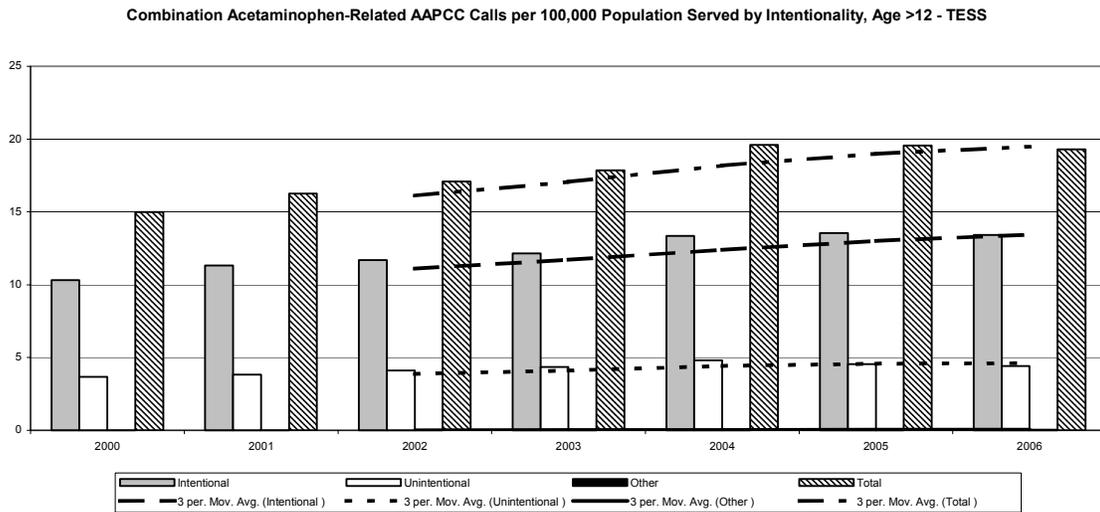


Figure 8 presents the rate of calls for *combination-ingredient* acetaminophen products for 2000 to 2006 by intentionality and overall. Similar to the overall pattern in Figure 6, calls for *combination-ingredient* acetaminophen products show a slight increase in the total rate of calls per year over time, from 15.0 in 2000 to 19.3 in 2006. Overall, 69% of calls were for intentional ingestions; unintentional ingestions accounted for 24% of calls, and the number of calls was stable over time.

Figure 8



In summary, the above figures provide evidence that poison control center calls relating to unintentional ingestions of acetaminophen products have remained stable since 2000.

4.5.2.6 *The 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 in the Proposed Rule 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 [17], 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. This report appears to be for a period six-months longer than reported at the NDAC meeting, and included additional cases with ages of 12 through 14 years. 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.

4.5.2.6.1 *McNeil's Review and Limitations of Data - AERS*

In the Proposed Rule [71 FR 377314 at 77321], FDA acknowledged the limitations of AERS data. These include unreliable dosing information, unreliable information on intentionality (cases thought to be unintentional may not have been due to stigma associated with reporting suicides), and the inability of cause to be determined with certainty from case reports. In addition, reporting to AERS may be sensitive to external events, eg, news reports that might heighten one's awareness and affect reporting. As with many other case reports or case series, there is no objective verification of the report and thus no certainty that the drug caused the event, the amount of the ingestion, or the use of concomitant medications. In addition, the presence of underlying disease or alcohol abuse could impact on the event. Despite these limitations, considerable weight appears to have been placed on information provided from AERS.

4.5.2.6.2 *McNeil's Updated Analysis 2000 to 2004 - AERS*

AERS data for the period 1999 to 2006 were reviewed for MedDRA terms contained within the standard MedDRA query for hepatic failure, cirrhosis and fibrosis. Reports were included if acetaminophen was listed as a suspect drug; reports of suicide or self-injury were excluded. A total of 830 cases were retrieved from AERS reporting use of OTC acetaminophen-containing products and 271 reporting use of prescription products containing acetaminophen. Fifty-six (56) of the cases reported use of both an OTC and prescription product containing acetaminophen. Figure 9 shows the number of reports containing MedDRA terms from the standard MedDRA query for hepatic failure, cirrhosis, and fibrosis for those 12 years of age and older by year, including a three-year moving average. Although cases with obvious intentional self-injury were excluded, it is possible that some cases included in Figure 9 may have been suicide related. The number of cases reporting use of prescription products containing acetaminophen, OTC single-ingredient or combination products containing acetaminophen, and use of both prescription and OTC products containing acetaminophen are provided. These data indicate some variability in the reporting of hepatic events with acetaminophen products to AERS over time. However, a stable pattern is observed for OTC products from 2004 to 2006.

Figure 9

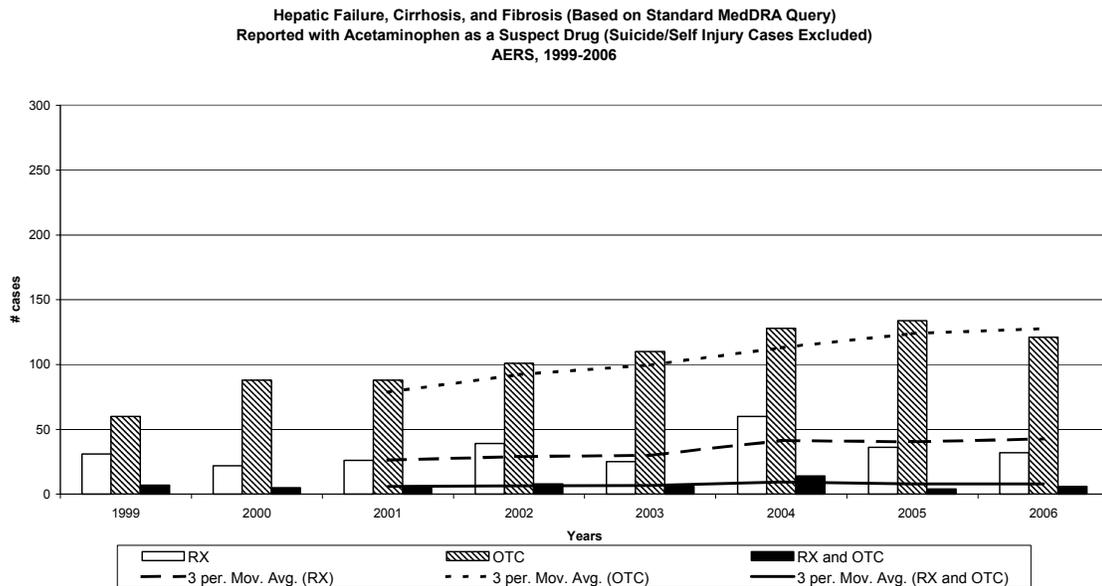
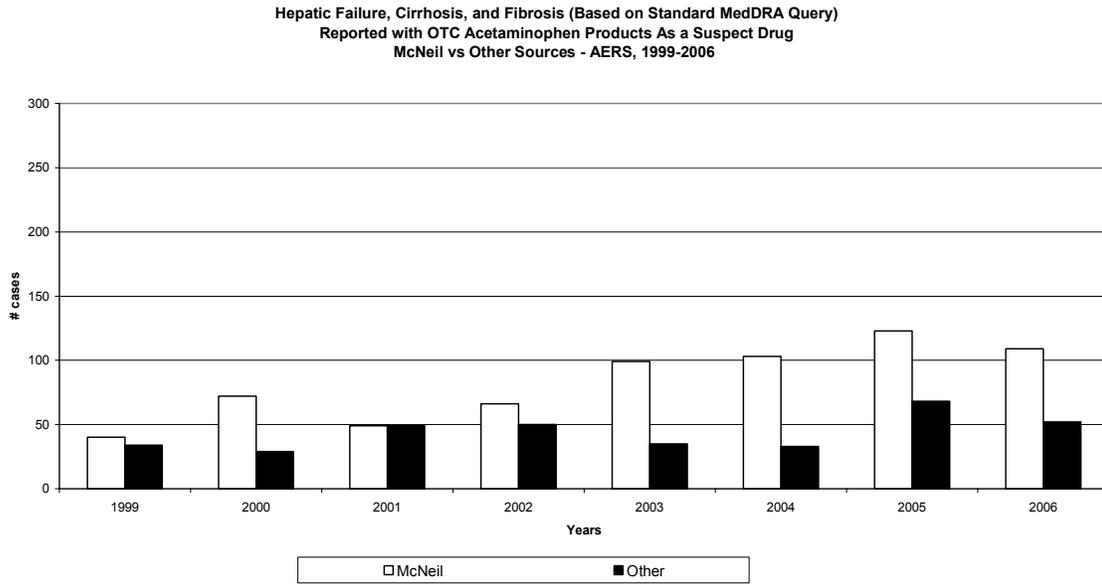


Figure 10 provides data on cases containing the MedDRA terms from the standard MedDRA query for hepatic failure, cirrhosis and fibrosis with OTC acetaminophen products listed as a suspect drug from AERS for the period 1999 to 2006, further subdivided into reports submitted by McNeil versus reports submitted by other companies. A stable consistent number of events have been reported by McNeil for the years 2003 to 2006.

Figure 10



4.5.2.7 *Summary of McNeil's Recent Analyses*

More recent analyses performed by McNeil using updated information from databases reviewed by FDA indicate that cases of acetaminophen overdose, acetaminophen-associated hepatotoxicity, and acetaminophen-associated death, whether intentional or unintentional, are not increasing.

- The number of acetaminophen-related emergency room visits decreased from 2000 through 2004 compared with 1993 through 1999 (NHAMCS).
- The number and age-adjusted rate of hospitalizations with unintentional acetaminophen overdose represent a small proportion of all hospitalizations with acetaminophen overdose, and occur with low frequency. The rate of hospitalization with unintentional overdose did not increase during the period from 2000 to 2004 (NHDS).
- The number of deaths (458) FDA cites as being at least in part attributed to acetaminophen is an overestimate. Only 12% of these cases were reported to have ALF and at least a third had another drug listed as an underlying cause of death (MCOD).
- In the years since 1999 when ICD-10 codes were initiated, the rate of age-adjusted ALF mortality and acetaminophen-associated ALF mortality, have not shown an increasing trend (MCOD).
- Most calls to poison centers for acetaminophen are for acute accidental ingestion in children and are related to exploratory ingestions or exposures. Since 2002, for adults and children older than 12 years of age, most calls to poison centers for acetaminophen were reported as intentional ingestion; unintentional acetaminophen ingestion represented a small proportion of calls for this age group and has not increased over time (TESS).
- A stable pattern of reporting was observed for hepatic events involving OTC acetaminophen products as a suspect drug in non-suicide cases during the years 2004 through 2006 (AERS).

4.6 Monitoring to Assess the Effect of Labeling Changes

Monitoring to assess the effect of labeling changes is important and should be tailored to targeted events, eg, unintentional overdose. The databases reviewed in Section 4.5.2 are not the ideal way to monitor the incidence of acetaminophen-associated events in the US, due to their inherent limitations as large case series. Given the difficulties with accurately assessing unintentional overdose, it is important to consider other surrogate endpoints. For example, before and after surveys could be conducted to monitor changes in behavior, knowledge, and awareness of acetaminophen use, in order to assess the effect of any future labeling changes.

Ongoing registries of cases should be modified to include a control series. For example, the ALFSG database could include a control group that could be used as a comparison for acetaminophen exposure in individuals who do not develop ALF. A potential source of controls could be a spouse or adult family member who has similar environmental exposures as the ALF cases. Information regarding other preexisting medical conditions, and other risk factors, including use of alcohol or other medications, could also be ascertained and compared between the ALF cases and controls. Alternatively, other more comprehensive databases could be developed with a comparison group included.

The use of pharmacy and HMO databases may be helpful to provide information about use of acetaminophen products as well as insurance claims pertinent to ALF. The information obtained from these sources, as well as the sources reviewed in this response, could be reviewed to evaluate if there is consistency across the different monitoring systems, and to describe trends over time in acetaminophen-associated hepatotoxicity.

FDA should partner with interested industry and academic stakeholders to review, discuss, and develop the most appropriate assessment tools and databases to evaluate acetaminophen-associated hepatotoxicity. McNeil is available and more than willing to participate in such an effort.

4.7 Reference List

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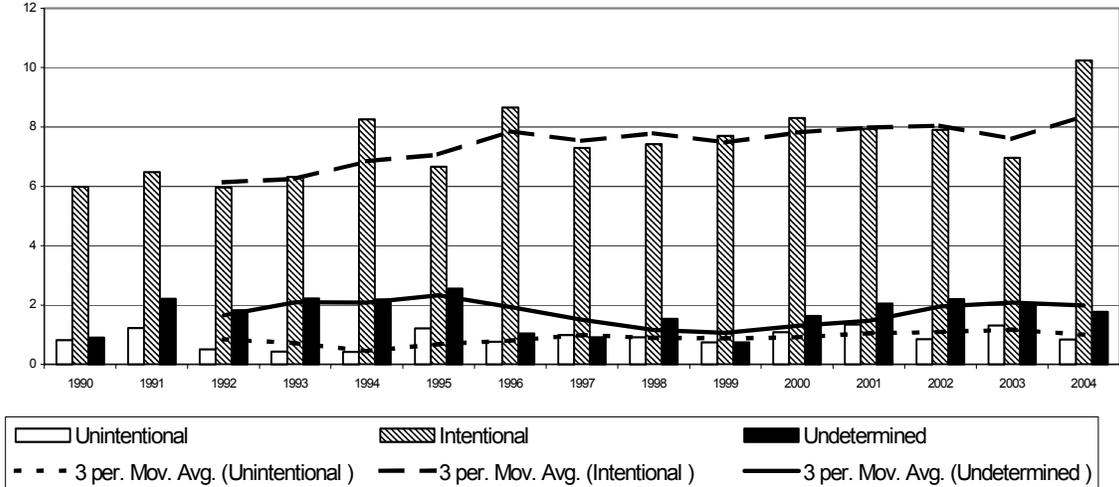
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SECTION 4 ATTACHMENT

SECTION 4, ATTACHMENT 1: SUPPLEMENTAL FIGURES

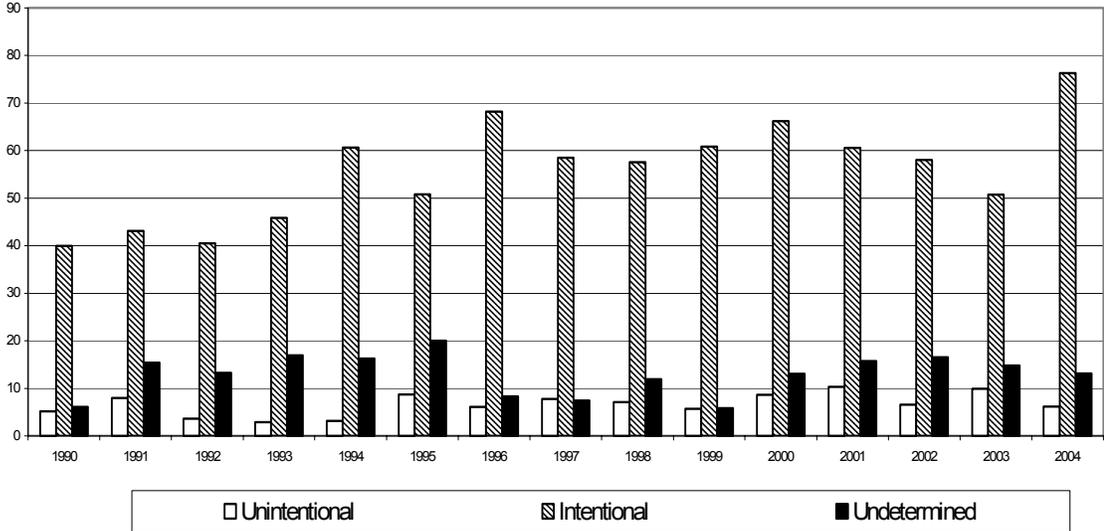
Supplemental Figure 1

NHDS: Age Adjusted Rate of Acetaminophen-Related Hospitalizations by Intentionality
per 100,000 US Population



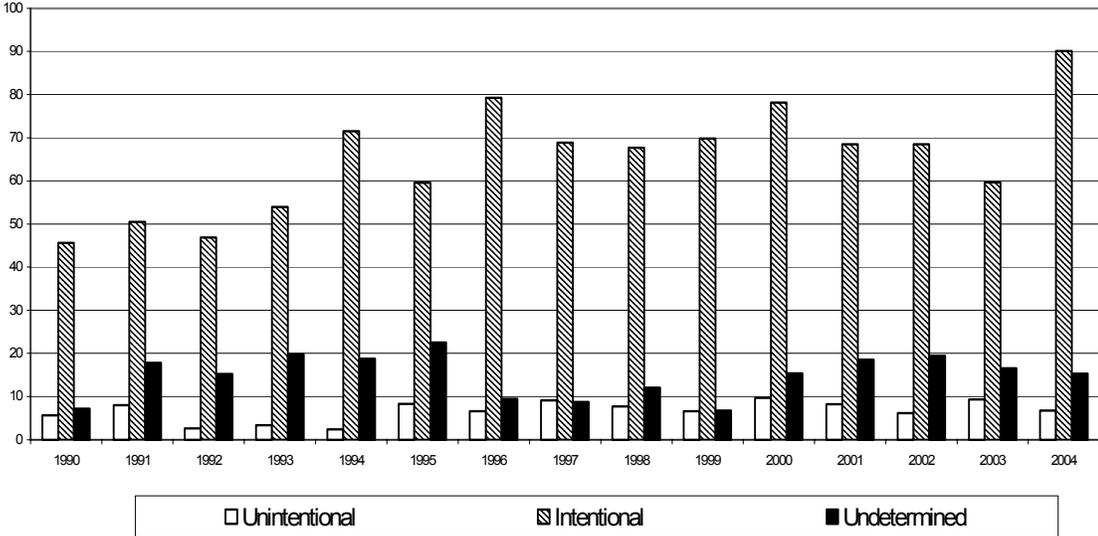
Supplemental Figure 2

NHDS: Age Adjusted Rate of Acetaminophen-Related Hospitalizations by Intentionality
per 100,000 Hospitalizations



Supplemental Figure 3

NHDS: Age Adjusted Rate of Acetaminophen-Related Hospitalizations by Intentionality
per 100,000 Hospitalizations (Age 10 or More Years)



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5. CHARACTERIZATION OF LIVER SAFETY: ROLE OF ACETAMINOPHEN METABOLISM

5.1 FDA Comments from the Proposed Rule

FDA issued to Docket No. 77N-0094, an OTC Drug Clinical Review for Monographs entitled, "Literature review to assess whether acetaminophen can be used safely by people with liver disease", on March 3, 2003. Publications from 1966 to January 2003 were reviewed. In this review, which is reference 26 of FDA's proposed rule, FDA writes (p 2):

"However, the hepatotoxic risk of acetaminophen in patients with pre-existing or underlying liver disease is unclear and there has been no special warning in the labels of acetaminophen products to alert consumers. This issue was discussed in the Nonprescription Drug Advisory Committee (NDAC) meeting on September 19, 2002, but the NDAC did not make a specific recommendation about this issue with regard to a liver warning. In this review, extensive literature searching has been conducted to justify our proposed warning change in the label".

As part of the executive summary of this review, FDA writes:

"In fact, post-market data analyses from the Office of Drug Safety at CDER and case study reports from literature suggest a strong signal that a history of liver disease may result in increased susceptibility to liver damage from acetaminophen. The following lines of evidence support the theory that patients with liver disease may be at risk when using acetaminophen products at therapeutic doses.

1. Hepatic glutathione conjugation with toxic metabolite of acetaminophen is a critical detoxification pathway of acetaminophen. Depletion of hepatic glutathione has been found in both alcoholic and non-alcoholic liver diseases, suggesting that the dysfunctional liver has less capacity to inactivate the toxic metabolite of acetaminophen.
2. Metabolite activation mediated by hepatic P450 enzymes, mainly P450-2E1, is required for acetaminophen to induce hepatotoxicity. Expression of hepatic P450-2E1 tends to increase in stable chronic liver diseases, particularly in the non-alcoholic fatty liver disorder with benign and indolent process and with increasing incidence. This suggests that a diseased liver has at least the same capacity as the normal liver to activate acetaminophen.
3. The capacity of hepatic glucuronide and sulfate conjugation, a major elimination pathway (>90%) of acetaminophen, tends to decrease in patients with chronic liver disease."

5.2 McNeil's Position

The experimental and clinical data that FDA summarized in the literature review cited in the FDA's proposed rule were incomplete, and these and other available data do not support the supposition of risk of acetaminophen hepatotoxicity in individuals with liver disease at therapeutic doses.

McNeil has taken two approaches to questions raised by FDA over four years ago at the September 19, 2002 meeting of the Nonprescription Drug Advisory Committee. One is to analyze the literature published up to April 2007, and the other is to sponsor several clinical acetaminophen studies that directly address the issues of critical importance. The experimental and scientific data that are counter to the hypothesis of risk of acetaminophen hepatotoxicity in liver disease and with alcohol use is provided below in this section, and the new clinical data on acetaminophen in individuals with liver disease and in alcohol users and abusers are provided in Item 1, Sections 6 and 7, respectively.

5.3 Key Points of Experimental and Scientific Data

- The literature on the disposition and toxicity of acetaminophen is voluminous and evolving. Suppositions (hypotheses) that might have made sense at one point in the history of this literature are no longer tenable when newer findings and insight are taken into account. Particularly in light of new and more sophisticated evidence of the role of critical cytochrome P450 isoforms, hepatocellular glutathione homeostasis, and glucuronyl- and sulfotransferase systems, the suppositions regarding risks in liver disease are theoretical in nature.
- 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 [1]
- Suppositions that adults with liver disease may be at risk due to differences in glutathione concentrations or CYP2E1 activity are often based on considering changes to each system involved in activation or detoxification in isolation [2]. They fail to recognize that both glutathione concentrations and CYP2E1 activity can change in the same direction in a given condition. Specifically,

- Adults with chronic hepatitis C infection have hepatic glutathione concentrations and CYP2E1 activity measured clinically within normal ranges. Production of plasma glutathione concentrations in chronic hepatitis C patients who have progressed to cirrhosis is slower. However, clinical metabolism studies show that CYP2E1 activity is likewise decreased in adults with hepatocellular cirrhosis. The balance does not appear to shift; thus, acetaminophen is no less safe in hepatitis C, even when it has progressed to cirrhosis.
- Adults with alcoholic liver disease who continuously consume alcohol have lower plasma and hepatic glutathione concentrations. Although alcohol induces *in vivo* CYP2E1 activity, it also acts as competitive inhibitor for CYP2E1, thereby effectively diminishing the oxidation of acetaminophen to NAPQI while present. Adults with alcoholic liver disease who abstain from consuming alcohol have both lower hepatic glutathione and *in vivo* CYP2E1 activity with increasing severity of disease.
- Adults with nonalcoholic fatty liver disease (NAFLD) have modest increases or decreases in hepatic glutathione concentrations. The clearance of chlorzoxazone, which is widely accepted as an *in vivo* probe of CYP2E1 activity, is increased in adults with NAFLD when expressed as in absolute terms, that is, not expressed relative to body size. Acetaminophen metabolism studies also show that clearance increases with body weight in young healthy and obese adults, but animal and clinical data show that this increase is due to higher glucuronide conjugating capacity of the liver at heavier weights, not acetaminophen activation.
- Adults with liver cirrhosis of various etiologies may have a slower rate of glutathione production; however, expression and *in vivo* activity of CYP2E1 also declines as chronic liver disease (both hepatocellular and cholestatic) progresses to moderate and severe cirrhosis. Again, the balance between activation and detoxification is sustained by simultaneous compensating changes.
- Experimental and clinical data show that glucuronidation is preserved in liver disease with evidence that UDP-glucuronosyltransferase may be up regulated in the remaining viable cells. Although experimental research on sulfation is sparse and does not differentiate among etiologies of liver disease, data from seven

acetaminophen metabolism studies unequivocally show that the amounts of glucuronide and sulfate metabolites produced are the same as those in healthy adults. Again, the changes that have been observed do not result in detectable enhanced risk.

5.4 The Role 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 clearance in healthy young adults through induction of UDP-glucuronosyltransferase (UGT) when dosed repeatedly with 1000, 1500, and 2000 mg, totaling 4, 6, and 8 grams per day [3]. This result has been observed even more recently in healthy older adults and in adults with moderate hepatic impairment [4], although UGT enzyme induction in the latter group was more modest than in healthy younger adults. Interestingly, a comprehensive review of the historic literature revealed supportive evidence for acetaminophen induction of UGT enzymes [5,6,7], 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 the mechanism by which acetaminophen becomes toxic to hepatocytes has evolved into a well-established theory, the role of liver status in the safety of acetaminophen has been the subject of contentious scientific and medical debate. Principle topics include alcohol use, fasting, malnutrition, and preexisting liver disease. Few of these issues have been put to direct experimental examination in humans. Therefore, this section addresses science that has been learned primarily from experiments conducted *in vitro*, with animal models, and in humans using metabolite-probes for specific reactions relevant to acetaminophen disposition and safety.

In Item 1, Section 6 that follows, new and published data from several acetaminophen metabolism studies conducted in adults and children with liver disease are reviewed. The new data are available from an acetaminophen metabolism study [4] in adults with moderate hepatic impairment that was recently completed by McNeil. Additionally, clinical safety data from prospective studies and the use of acetaminophen by this special population are summarized.