EXECUTIVE SUMMARY

This is McNeil's background package on acetaminophen for the September 19, 2002 Nonprescription Drugs Advisory Committee Meeting that was announced in the *Federal Register* of August 20, 2002. This submission provides data and an evidence-based assessment of acetaminophen efficacy and safety.

Our assessment demonstrates the following key points:

- Access to OTC pain reliever and fever reducer medicines provides major benefit to millions of Americans.

- Each week, nearly 50 million adults in the United States take acetaminophen-containing products.

- Acetaminophen, at currently recommended doses, is used safely by adults, pediatric and elderly patients, as well as by patients with chronic renal disease or chronic stable liver disease.

- Review of metabolism, pharmacokinetic, and prospective clinical trial data confirms that there is no increased risk of toxicity at currently recommended doses of acetaminophen.

- The optimal effective adult analgesic dose of acetaminophen is 1000 mg every four to six hours, up to 4000 mg per 24 hours. This dosing frequency is supported by pharmacokinetic, clinical, and consumer use data.

- The AERS spontaneous reporting system serves as a signal generating system for rare, unexpected adverse events in marketed products. It cannot be used to determine event rates, dose, or intentionality.

- Case reports are the source of serious hepatic events associated with acetaminophen exposure. These reports are observational and therefore cannot be used to establish causality.

- Recent medication use surveys suggest that the vast majority of consumers use analgesics within the recommended OTC daily dose.

- McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:
    - the product ingredients
    - the proper dosing and proper use of medications
    - the importance of not taking more than the recommended dose
    - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
    - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

In summary,

- Acetaminophen, at currently recommended OTC doses, is safe and effective for adults and children, including the elderly and people with liver or kidney disease. Case reports, including AERS data, do not undermine this conclusion.

- As has been known for many years, a substantial untreated acetaminophen overdose can lead to serious health consequences.

- Through labeling changes and educational programs, McNeil is committed to minimizing any product misuse leading to overdose.

- If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.

TABLE OF CONTENTS

1 INTRODUCTION

McNeil Consumer & Specialty Pharmaceuticals (McNeil), a member of the Johnson & Johnson family of companies, submits this background package for the Nonprescription Drugs Advisory Committee (NDAC) meeting scheduled for September 19, 2002.

McNeil markets Tylenol® (acetaminophen) and Motrin® (ibuprofen) single-ingredient and combination-ingredient adult and pediatric products. In addition, McNeil markets St. Joseph® low strength (81 mg) aspirin that is intended for use by adults only.

KEY POINTS

Efficacy

- Treatment of pain provides tremendous benefit to many consumers. Consumers will self-treat pain and their selection of OTC analgesics will depend on availability, accessibility, and effectiveness of these products.

- A recent acute pain dose-response study demonstrates superior efficacy of acetaminophen 1000 mg compared to both acetaminophen 500 mg and placebo.

- Pharmacokinetic-pharmacodynamic modeling predicts that plasma concentrations following a 1000-mg dose of acetaminophen are consistently at or above the EC_{50} needed for optimal pain relief. Although development of the model was not based on a 650-mg dose of acetaminophen, plasma concentrations of a 650-mg dose of acetaminophen consistently fall below the EC_{50}. These findings, integrated with the data from the meta-analysis and placebo-controlled studies demonstrate that the optimal effective adult analgesic dosing of acetaminophen is 1000 mg every four to six hours, up to 4000 mg per 24 hours.

- A dosing frequency for acetaminophen of every four to six hours up to 4000 mg daily is supported by pharmacokinetic, clinical and consumer use data indicating both that the majority of subjects remedicate in this time frame and that the analgesic duration effect lasts between three to five hours.

Pharmacokinetics

- Acetaminophen pharmacokinetics, which have been thoroughly characterized by prospective well-controlled studies, are consistent and predictable over a wide range of single doses. Therefore, the amount of acetaminophen in the body (and plausible corresponding doses) can be reliably estimated from a plasma concentration(s) measured at a known time following acute acetaminophen ingestion.

- Prospective pharmacokinetic studies show that with repeat doses of 1 and 1.5 g (4 and 6 g/day) acetaminophen plasma concentrations reach steady-state levels within 10 to 15 hours and do not accumulate to higher levels with continued dosing. These results are consistent with the short elimination half-life of two to three hours for acetaminophen and the recommended dosing interval of four to six hours.

Metabolism

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

- The oxidative intermediate, NAPQI, which is mainly generated by CYP2E1 oxidation, is not measurable due to its high reactivity and *instantaneous conjugation with glutathione*. NAPQI may potentially cause hepatotoxicity after a substantial acute overdose; however, glutathione is present in sufficient quantities to conjugate the small amount of NAPQI following therapeutic acetaminophen doses. Additionally, the body continuously replenishes glutathione. As a result, liver toxicity does not occur at normal therapeutic doses.

- With repeat doses of 0.65 and 1 g acetaminophen every six hours, steady-state concentrations of the glucuronide conjugate are higher, and those for the sulfate, cysteine, and mercapurate conjugates are all lower than what would be predicted from single dose data. These findings indicate time-dependent changes in acetaminophen metabolism during repeat dosing, which may reflect up- and/or down-regulation of the different enzymatic pathways.

Special Populations

- Acetaminophen, at currently recommended doses, is used safely by adults, pediatric and elderly patients, as well as by patients with chronic renal disease or chronic stable liver disease. Review of metabolism pathways suggests that there is not an increased risk of toxicity at currently recommended doses of acetaminophen.

Serious Adverse Event Reports

- The AERS spontaneous reporting system serves as a signal generating system for rare, unexpected adverse events in marketed products. It cannot be used to determine event rates, dose, or intentionality.

- Case reports are the source of serious hepatic events associated with acetaminophen exposure. These reports are observational and therefore cannot be used to establish causality.

- The number of serious reports for acetaminophen products at the FDA is disproportionately large relative to other monograph analgesics because: a) FDA regulations do not require AERS reporting for OTC monograph drug products, and b) McNeil has submitted serious reports for all single-ingredient acetaminophen products and reports of death for acetaminophen combination products, including published literature and fatalities from AAPCC.

- Data from AAPCC, DAWN and liver transplant centers are consistent, and show that intentional suicide is the most frequent reason for adult acetaminophen overdose.

Consumer Medication Use

- Recent medication use surveys suggest that the vast majority of consumers use analgesics within the recommended OTC daily dose.

- Medication use surveys also provide insight regarding consumer analgesic use behaviors that may result in excessive OTC analgesic exposure.

- Based on review of surveys regarding consumer behaviors and other available data regarding misuse of OTC analgesics, McNeil proposes that labeling and educational interventions for enhancing proper consumer behaviors should be aimed at focusing the attention of all OTC medication users on:
    - the product ingredients
    - the proper dosing and proper use of medications
    - the importance of not taking more than the recommended dose
    - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
    - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

Risk Management Initiatives

- McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:
    - the product ingredients
    - the proper dosing and proper use of medications
    - the importance of not taking more than the recommended dose
    - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
    - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

- McNeil is also sponsoring an ongoing survey of consumer behaviors to monitor changes in consumer OTC analgesic use behaviors.

- Pediatric misadministration rarely results in serious outcome. Rare events could be further prevented by permitting dosage information for children under two on the product label.

Impact of Risk Management Initiatives

- Evaluation of acetaminophen risks, as with evaluation of NSAID risks, should include all doses that may be self-administered given consumer utilization patterns for OTC-available analgesics.

- If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.

2 EFFICACY OF ACETAMINOPHEN IN THE TREATMENT OF PAIN

KEY POINTS

- Treatment of pain provides tremendous benefit to many consumers.
- A recent acute pain dose-response study demonstrates superior efficacy of acetaminophen 1000 mg compared to both acetaminophen 500 mg and placebo.
- In addition to individual study data which demonstrate acetaminophen 1000 mg has superior efficacy when compared to acetaminophen 650 mg and 500 mg, the results of a systematic review and meta-analysis demonstrate the statistically significant superior efficacy of acetaminophen 1000 mg over acetaminophen 600/650 mg in the relief of pain.
- Pharmacokinetic-pharmacodynamic modeling predicts that plasma concentrations following a 1000-mg dose of acetaminophen are consistently at or above the EC_{50} needed for optimal pain relief. Although development of the model was not based on a 650-mg dose of acetaminophen, plasma concentrations of a 650-mg dose of acetaminophen consistently fall below the EC_{50}. These findings, integrated with the data from the meta-analysis and placebo-controlled studies demonstrate that the optimal effective adult analgesic dosing of acetaminophen is 1000 mg every four to six hours, up to 4000 mg per 24 hours.
- A dosing frequency for acetaminophen of every four to six hours up to 4000 mg daily is supported by pharmacokinetic, clinical and consumer use data indicating both that the majority of subjects remedicate in this time frame and that the analgesic duration effect lasts between three to five hours.
- Acetaminophen in prescription combination medications provides added effectiveness over the individual components given separately.

2.1 Benefits of Pain Treatment

Pain is widely recognized as a condition that merits appropriate pharmacological and non-pharmacological treatment. Recent guidelines and standards for the assessment and treatment of pain have been issued, including those by accrediting organizations [JCAHO 2001]; state, federal, and international agencies[1]; and medical associations[2]. These guidelines and standards are predicated upon the acceptance of the individual's right to receive appropriate assessment and treatment for their pain.

This recent emphasis on appropriate pain treatment is fueled by a substantial body of research demonstrating that under-treatment of pain results in considerable costs to patients[3] (eg, the deterioration of physical and psychological health), families (eg, increased social isolation and caregiver distress) [Snelling 1994; Miaskowski 1997], and healthcare institutions[4] (eg, substantial healthcare utilization and costs). Research also documents the staggering costs of pain borne by society. In a survey examining the impact of pain in the American workplace, investigators found that painful conditions accounted for 50 million sick days per year at an annual cost of $3 billion in excess wages [Louis Harris 1996]. Additional costs include wages required to replace absent workers, and disability and worker's compensation claims. The most common types of pain resulting in absenteeism were headaches and menstrual pain (each affecting 40 million workers), low back pain (affecting 36 million workers), muscle pain (affecting 24 million workers), and neck pain (affecting 20 million workers). As a result, the socioeconomic ramifications of these "everyday" types of pain are extensive and affect the society at large.

Given these extensive patient, family, healthcare institution and socioeconomic costs, a U.S. Federal law was passed in 2001 (U.S., H.R. 3244 Title VI, Sec. 1603), which provided for the "Decade of Pain Control and Research" to begin January 1, 2001. This Congressionally declared "Decade" (the second medical decade in U.S. history ever to be

---

[1] Agency for Healthcare Research and Quality [2001]; World Health Organization [1990]; Veterans Health Administration [1999]; Washington State [1999].

[2] American Academy of Pediatrics [2000]; American College of Radiology [1999]; American Geriatric Society [1998]; American Medical Directors Association [1999]; American Pain Society [1999]; American Society of Anesthesiologists [1997]; American Academy of Orthopedic Surgeons [1996]; Silberstein [1999].

[3] BenDebba [1997]; Carr [1999]; Casten [1995]; Cousins [1994]; Desbiens [1997]; Dworkin [1997]; Foley [1995]; Gottschalk [1998]; Heim [1993]; Katz [1995, 1996]; Liebeskind [1991]; Linton [1997]; Liu [1995]; McCaffrey [1999]; Page [1996]; Sheehan [1996]; Tasmuth [1995].

[4] Ferrell [1994]; Furdon [1998]; Grant [1995]; Gureje [1998]; Riley [1996].

declared by Congress), is heralded by both pain specialists and advocates alike as bringing a much-needed focus on pain control to both the public and private sectors, and as the first step in stimulating further progress in pain-related research, education and clinical treatment.

As such, it is very important for the everyday aches and pains experienced by people in all walks of life to be adequately treated. Acetaminophen, at doses up to 4000 mg per day, is considered to be beneficial in the treatment of mild to moderate pain due to its favorable efficacy and safety profile [Amadio 1984].

2.2 Well-Established Efficacy

The efficacy of acetaminophen for the temporary relief of aches and pains and for the reduction of fever has been well established in over 150 placebo-controlled clinical trials. These studies examined a variety of pain, using these models: dental pain (n=76), surgical pain (n=38), headache/migraine pain (n=19), osteoarthritis (n=3), menstrual pain (n=2), and other painful conditions (n=13). In 1977, the Advisory Review Panel on OTC Internal Analgesic, Antipyretic and Antirheumatic Products concluded that acetaminophen was a safe and effective OTC analgesic when taken in an adult dosage of up to 1000 mg, not to exceed 4000 mg in 24 hours for no longer than ten days. This same dose was reaffirmed in 1988, when FDA published the Tentative Final Monograph (TFM) for OTC Internal Analgesic, Antipyretic and Antirheumatic Products.

Important to this review is a discussion of the appropriate dose of acetaminophen. Several dosage levels have been studied. The most common regimen is 1000 mg given every four to six hours up to four doses (4000 mg) per day. The next most common regimen is 650 mg given every four hours up to six doses (3900 mg) per day. Data demonstrate that consumers get more effective pain relief of a longer duration with single doses of 1000 mg compared to a dose of 650 mg or to a dose of 500 mg.

2.2.1 Comparative Efficacy of Acetaminophen 1000 mg Versus 500 mg – From Individual Clinical Trials

A recent acute dose-response study was performed in a postoperative dental pain model that demonstrated the superior efficacy of acetaminophen 1000 mg compared to acetaminophen 500 mg [Nick 2002]. The primary efficacy endpoint, TOTPAR4[5], for

[5] Total pain relief over four hours.

acetaminophen 1000 mg was significantly superior to acetaminophen 500 mg ($p<0.0001$) and revealed that approximately 42% more pain relief was provided by the 1000-mg dose compared to the 500-mg dose. The superiority of acetaminophen 1000 mg compared to acetaminophen 500 mg was also demonstrated with all other endpoints.

Three other studies utilizing post-oral surgery pain models [Seymour 1996; Nystrom 1988; Quiding 1984] and one study utilizing a post-orthopedic surgery pain model [McQuay 1986] also demonstrate the superior efficacy of acetaminophen 1000 mg compared to acetaminophen 500 mg.

2.2.2 Comparative Efficacy of Acetaminophen 1000 mg Versus 600/650 mg – From Systematic Review and Meta-Analysis

An important review of acetaminophen, comparing the relative efficacy of various acetaminophen doses, is a meta-analysis conducted by the University of Oxford. In a recent publication, McQuay et al [McQuay 2002] identified 46 randomized, placebo-controlled clinical trials of subjects with postoperative pain of moderate-to-severe intensity evaluated over a four- to six-hour treatment period. An overall estimate of the efficacy of two acetaminophen doses (600/650 mg and 1000 mg) was provided. In these trials, 2561 subjects received acetaminophen and 1625 subjects received placebo [McQuay 2002]. The number-needed-to-treat (NNT) was one of the endpoints used for this meta-analysis and was defined as the number of subjects required to receive a particular acetaminophen dose in order for one subject to achieve at least 50% pain relief at that dose compared with placebo over a four- to six-hour treatment period. The lower the NNT, the more effective the acetaminophen dose.

Table 2-1. Meta-Analysis Results for Single-Dose Efficacy of Acetaminophen 1000 mg and 600/650 mg Compared with Placebo [McQuay 2002]

		At least 50% pain relief with		
		Acetaminophen	Placebo	
Number of Trials	Dose (mg)	N (%)	N (%)	NNT (95% CI)
23	1000	701/1527 (46)	197/1032 (19)	3.7 (3.3 - 4.3)
18	600/650	250/614 (41)	131/593 (22)	5.4 (4.2 - 7.4)

As shown in Table 2-1, the NNT for acetaminophen 1000 mg is 3.7 and the NNT for acetaminophen 600/650 mg is 5.4, indicating that acetaminophen 1000 mg has superior efficacy compared to 650 mg. Although the confidence intervals overlap slightly for the two doses, the NNT values for acetaminophen 1000 mg and 600/650 mg are significantly different ($z = 2.59$ and $p = 0.009$). The marginal overlap of the confidence intervals in this comparison of more than 3700 subjects underscores the difficulty of showing significant dose-response differences between doses at less than two-fold increments with oral analgesics in small individual clinical trials.

2.2.3 Comparative Efficacy of Acetaminophen 1000 mg Versus 650 mg – From Individual Clinical Trials

Three placebo-controlled studies specifically compared acetaminophen doses of 1000 mg and 650 mg [Hopkinson 1974; McNeil 1972; Yuan 1998]. These trials report greater efficacy of acetaminophen 1000 mg compared to acetaminophen 650 mg. Two of these studies [Hopkinson 1974; McNeil 1972] were submitted to the FDA as part of Amendment 1, dated December 19, 1972, to NDA 17-053 for Extra Strength Tylenol® acetaminophen 500 mg, and were the two clinical trials which were the basis of FDA approval for the NDA. These three studies were not included in the meta-analysis conducted by McQuay et al [McQuay 2002].

2.2.4 Comparative Efficacy of Acetaminophen 1000 mg Versus 2000 mg – From An Individual Clinical Trial

The efficacy of acetaminophen 1000 mg has also been demonstrated compared to acetaminophen 2000 mg. One placebo-controlled post oral surgery pain study comparing acetaminophen 1000 mg to 2000 mg did not show statistically significantly greater pain relief of acetaminophen 2000 mg compared to acetaminophen 1000 mg [Skoglund 1991]. This study suggests that there is no significant analgesia benefit beyond an acetaminophen 1000 mg single dose.

2.3 Pharmacokinetic-Pharmacodynamic Model

Pharmacokinetic-pharmacodynamic (PK-PD) modeling predicts that a 1000-mg dose of acetaminophen yields plasma concentrations consistently above the EC_{50}[6] that is needed to provide optimal pain relief. These PK-PD results are consistent with the meta-analysis

[6] concentration that elicits 50% of the maximum drug response

[McQuay 2002] of acetaminophen efficacy studies and placebo-controlled studies [Hopkinson 1974; Yuan 1998] that reported greater efficacy of 1000 mg acetaminophen compared with lower single doses.

A substantial body of research documents acetaminophen's pharmacokinetic properties and clinical efficacy. Integrating these study data with acetaminophen PK/PD modeling demonstrates that the optimal effective adult analgesic dosing of acetaminophen is 1000 mg every four to six hours, up to 4000 mg per 24 hours.

2.3.1 Modeling Reveals Effective Concentration for Analgesic Response

The PK-PD relationship of acetaminophen was determined for postoperative analgesia in adults following molar extraction. A population PK-PD model [Hutcheson 1993] was developed using data from 114 outpatients, who received a single dose of 1000 mg acetaminophen (either caplet or effervescent solution) or placebo, at the onset of significant pain following surgical extraction of impacted third molars. The other PK-PD model [Gelotte 1995] used data from a bioavailability and dental pain study in male subjects, who received either two doses of 650 mg immediate-release acetaminophen four hours apart or one dose of 1300 mg extended-release acetaminophen.

Similar to other analgesics, both studies found that the analgesic effect (pain relief and pain intensity scores) of acetaminophen lags behind plasma concentrations over time. Thus, an "effect" compartment was used to link pharmacokinetic and pharmacodynamic models. This effect compartment adjusts for the chronological aspects of acetaminophen effect, which may depend on physicochemical (eg, diffusion, partitioning) and/or physiological (eg, perfusion, receptor binding) processes that relate drug in plasma to drug at its site of action.

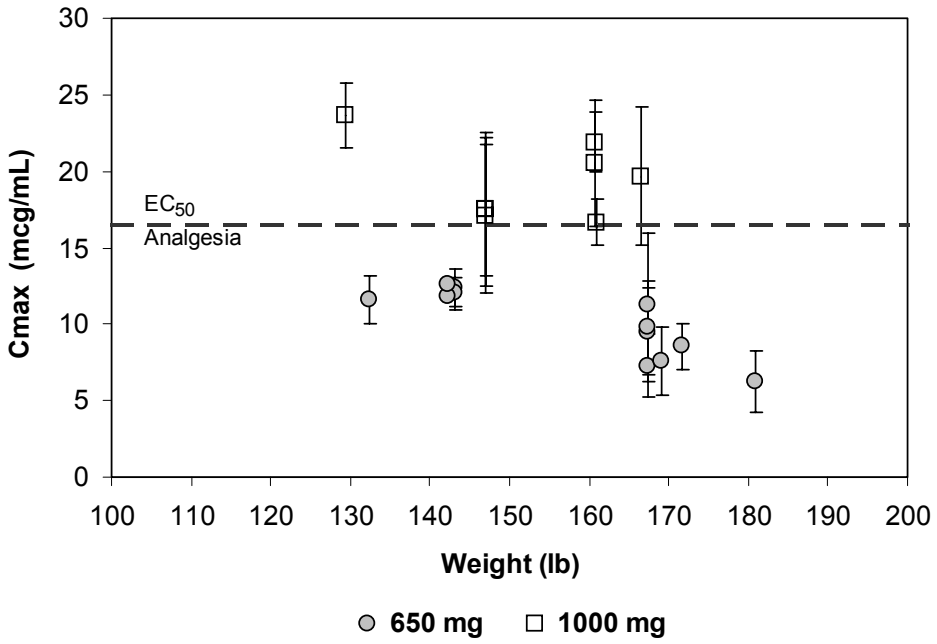
Estimates of the pharmacodynamic parameters obtained for acetaminophen analgesia were essentially the same for both studies. In particular the EC_{50} (effectiveness concentration that elicits 50% of the maximum drug response) was estimated at 15.2 μg/mL [Hutcheson 1993] and 16.55 μg/mL [Gelotte 1995] for acetaminophen.

2.3.2 The 1000-mg Dose Yields Acetaminophen Concentrations Needed to Provide Adequate Pain Relief

To further assess the relationship between acetaminophen dose and resultant plasma concentrations needed to elicit analgesic response, the EC_{50} from the PK-PD models was

considered with regard to plasma data from 18 PK studies[7] for the 650- and 1000-mg doses. Figure 2-1 shows the mean C_{MAX} values for both doses relative to the EC_{50} for acetaminophen. These findings support that the 1000-mg dose of acetaminophen yields optimal plasma concentrations needed to provide adequate pain relief.

Figure 2-1. Study Mean C_{MAX} By Dose Relative to EC_{50} for Adult Analgesia



Factors such as body size, age, and physiology lead to differences in plasma concentrations among adults at a given dose. For example, maximum plasma concentrations of acetaminophen for the 1000-mg dose can fall below the EC_{50} threshold in larger adults, which is illustrated in Figure 2-2 with individual C_{MAX} values from patients in a dental pain study [Hutcheson 1993]. In addition, the lowest measured C_{MAX} values in this study were associated with the lower pain relief scores as seen in Figure 2-3. Based on the linear relationship between dose and C_{MAX}, the 650-mg acetaminophen dose is expected to result in similarly scattered C_{MAX} values with a greater percentage below EC_{50}.

[7] Bedjaoui [1984]; Rawlins [1977]; Ameer [1983]; Divoll [1982a,b,c]; Hindmarsh [1991]; Grattan [2000]; Jorup-Ronstrom [1986]; Kohli [1982]; Miners [1988]; Parier [1988]; Yiamouyiannis [1994]; Mitchell [1983]; Borin [1989]; Sajahawalla [1991]; Douglas [1996]; Stork [1996]; Christophersen [2002]; Green [2001].

Figure 2-2. Individual CMAX by Weight After a 1000-mg Acetaminophen Dose in a Dental Pain Study [Hutcheson 1993]

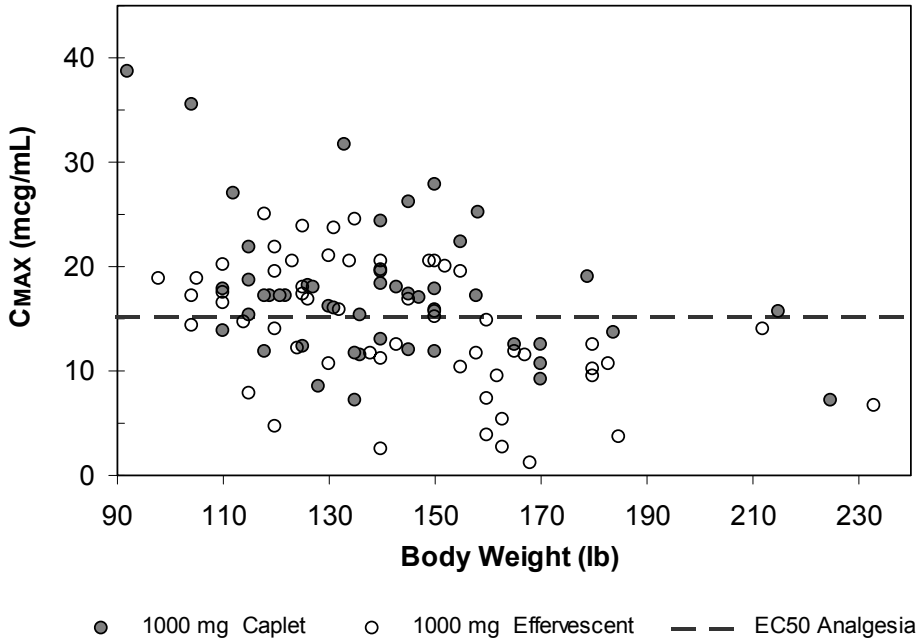
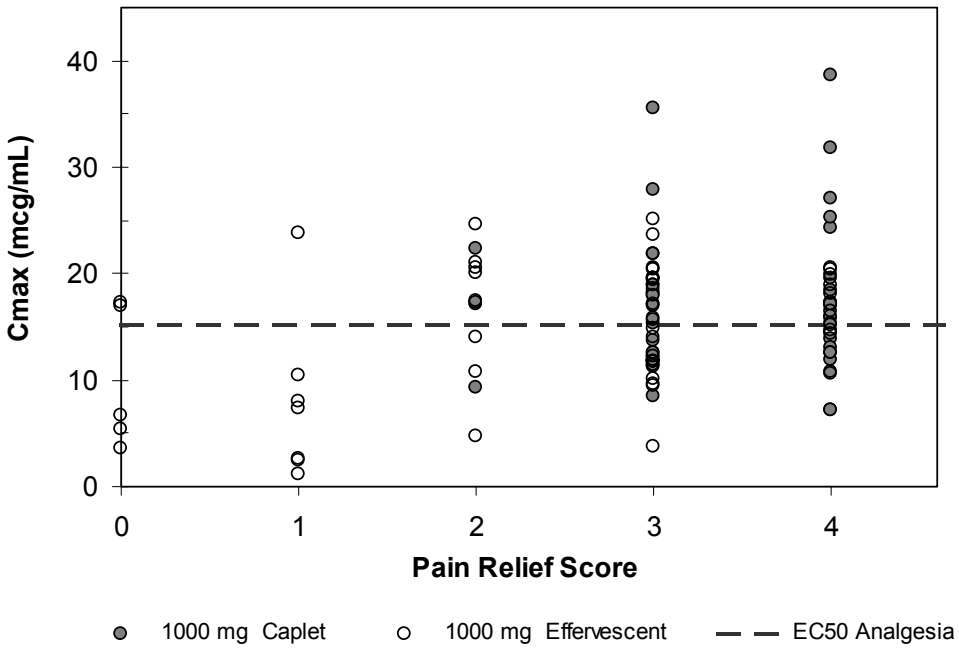


Figure 2-3. Individual CMAX and Maximum Pain Relief After a 1000-mg Acetaminophen Dose in a Dental Pain Study [Hutcheson 1993]



Pharmacokinetic-pharmacodynamic modeling predicts that plasma concentrations following a 1000-mg dose of acetaminophen are consistently at or above the EC_{50} needed for optimal pain relief. Although development of the model was not based on a 650-mg dose of acetaminophen, plasma concentrations of a 650-mg dose of acetaminophen consistently fall below the EC_{50}. These findings, integrated with the data from the meta-analysis and placebo-controlled studies demonstrate that the optimal effective adult analgesic dosing of acetaminophen is 1000 mg every four to six hours, up to 4000 mg per 24 hours.

2.3.3 Data on Frequency of Dosing

2.3.3.1 Dosing of Acetaminophen 1000 mg Every Four to Six Hours

It is important to consider dosing interval when discussing the efficacy of acetaminophen, because the need for pain relief often extends beyond the initial acetaminophen dose of 1000 mg. The four- to six-hour dosing interval for acetaminophen 1000 mg included in McNeil's current label is supported by pharmacokinetic and clinical data.

In a post oral surgery pain study, 59% of patients receiving acetaminophen 1000 mg remedicated within four hours, and 76% remedicated within six hours [Quiding 1984]. In addition, data from post oral surgery pain studies indicate that a large percentage of patients receiving an initial acetaminophen dose of 1000 mg required remedication four to five hours after the initial dose [Nystrom 1988; Quiding 1984; Gustafsson 1983; Pigeon 1992; Kiersch 1994; Mehlisch 1995]. The duration of a single dose of analgesia ranged from 3.1 to 4.8 hours in patients taking the acetaminophen 1000-mg dose in these studies.

The four-to-six hour dosing interval provides consumers with a practical and flexible dosing regimen to meet their pain relief needs within a variety of daily living schedules. Use of a four-to-six hour dosing interval provides the flexibility needed to conveniently coincide with most waking/breakfast, lunch, dinner, and bedtime medication use schedules. There are situations (eg, toothache or after oral procedures) in which additional analgesic relief may be needed as early as four hours after an initial dose. With this dosing regimen, consumers can be assured of both effective and consistent pain control.

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

Adult OTC acetaminophen product labeling includes the following statement concerning duration of use: Stop use and ask a doctor if pain gets worse or lasts for more than ten

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

Multiple doses of acetaminophen 1000 mg taken for three to ten days have shown superior efficacy compared to placebo in a variety of models including post oral surgery pain [Seymour 1983; Skjelbred 1979; Skjelbred 1984], arthritis pain [Altman 1999; Zoppi 1995], painful conditions [Nielsen 1991; Wade 1982], and dysmenorrhea [Haack 1986]. Acetaminophen was well tolerated and no serious adverse events were reported in any of the studies.

The safety and efficacy of acetaminophen when compared to placebo or NSAIDs for the treatment of pain for extended time periods has been demonstrated in five osteoarthritis trials involving a total of 896 patients [Amadio 1983, Haack 1986, Bradley 1991, Lee 1998, Geba 2002]. These studies show that acetaminophen, when taken at the recommended daily dose of up to 4000 mg per day, demonstrated efficacy and an acceptable safety profile. The number of subjects and duration of acetaminophen therapy (25 subjects for three weeks [Amadio 1983], 99 subjects for 4 weeks [Haack 1986], 61 subjects for 4 weeks [Bradley 1991], 52 subjects for 8 weeks [Lee 1998], and 94 subjects for 6 weeks [Geba 2002]) support the safe use of acetaminophen for extended periods of time. Results demonstrated that acetaminophen was superior to placebo and comparable to NSAIDs (such as ibuprofen, celecoxib, and naproxen) regardless of the number of participants or duration of therapy.

In addition, current clinical practice guidelines support acetaminophen use in adults at a dosage up to 4000 mg per day. In 1995, the American College of Rheumatology (ACR), and in 2000, the European League Against Rheumatism (EULAR) issued guidelines recommending acetaminophen, in daily doses up to 4000 mg, as the first line of pharmacologic therapy in the treatment of osteoarthritis pain [Hochberg 1995; Pendleton 2000]. Subsequently in 2000, the ACR issued the results of a detailed evidence-based-medicine approach used to develop updated recommendations for the medical treatment of osteoarthritis; this update provided continued support for acetaminophen use. The ACR approach gave the strongest weight to data from controlled trials and accommodated expert opinion as well [ACR Subcommittee on OA Guidelines 2000]. Also, the American Geriatrics Society Clinical Practice Guidelines for the Management of Chronic Pain in Older Persons

recommended acetaminophen as the drug of choice for relieving mild to moderate musculoskeletal pain [AGS 1998], and it remains the drug of choice in the current guidelines [AGS 2002].

2.4 Implication of Modifying Acetaminophen Dosing Regimen

Consumers take analgesic medications in single doses that provide them with adequate pain relief. For acetaminophen that dose is 1000 mg. It is the only approved dose in the United Kingdom. Products that provide this dose account for approximately 90% of products sold in the United States. If a dose lower than 1000 mg was the only approved dose, data suggest that analgesia would be inadequate or of limited duration for many individuals. Consequently, these individuals may re-dose, and if pain persists, take repeated doses, which compounds the identified existing consumer misuse behavior of individuals who may choose to ignore the maximum recommended dosage and continue to titrate to maximum analgesic effect [Carr 2002]. Alternatively, if consumers consistently find that the medication they are using does not provide adequate relief, they may switch to an alternative medication. This switch could have unintended negative public health consequences (see Section 4, Assessment of Acetaminophen Safety).

Reduction of the maximum 1000 mg acetaminophen single dose would be contradictory to the clinical and pharmacokinetic-pharmacodynamic data presented that demonstrate that the efficacy of acetaminophen is dose-related between 500 mg and 1000 mg and that acetaminophen 1000 mg is significantly more efficacious than acetaminophen 650 mg or 500 mg.

2.5 Added Effectiveness for Acetaminophen-Containing Prescription Combination Products

A number of prescription medications contain acetaminophen in combination with other analgesics. The use of a combination oral analgesic offers several benefits over the use of the individual components given separately. Combining analgesics into a single product may facilitate prescribing and compliance by reducing the total number of medications that a patient must take. Furthermore, combining products with different mechanisms of action provides multimodal coverage of the underlying pain pathophysiology allowing efficacy in a broad spectrum of pain syndromes as the individual agents act in an additive or synergistic fashion. Additionally, in terms of safety, lower doses of each individual analgesic used in the combination may result in a lower incidence of adverse effects attributable to an

individual analgesic component. An example of this can be demonstrated in the case of the tramadol/acetaminophen combination product.

2.5.1 Rationale for an Acetaminophen Combination Product

Tramadol hydrochloride (tramadol) is a centrally-acting analgesic that is widely marketed throughout the world. Tramadol has been shown to be effective in treating a wide variety of pain conditions, including the management of both nociceptive and neuropathic pain, when treatment with strong opioids is not required. The pharmacokinetic and pharmacodynamic profile of tramadol shows peak activity in two to three hours with an elimination half-life and duration of analgesia of about six hours. Acetaminophen yields peak plasma concentrations between 0.4 and 1 hour and has an elimination half-life of two to three hours. Combination of tramadol with a rapid-onset and short-acting analgesic such as acetaminophen, provides substantial patient benefit over either component alone. The clinical positioning of the tramadol/acetaminophen combination is for the treatment of moderate to moderately-severe pain with dosing as needed where rapid onset combined with prolonged analgesia is desirable.

ULTRACET™ contains 37.5 mg of tramadol hydrochloride and 325 mg of acetaminophen in a single tablet and is made by Ortho-McNeil Pharmaceutical, another member of the Johnson & Johnson family of companies. As of August 15, 2001, ULTRACET was approved for marketing in the United States for the short-term (5 days or less) management of acute pain, with a dosing regimen of two tablets every four to six hours as needed for pain relief, up to a maximum of eight tablets per day.

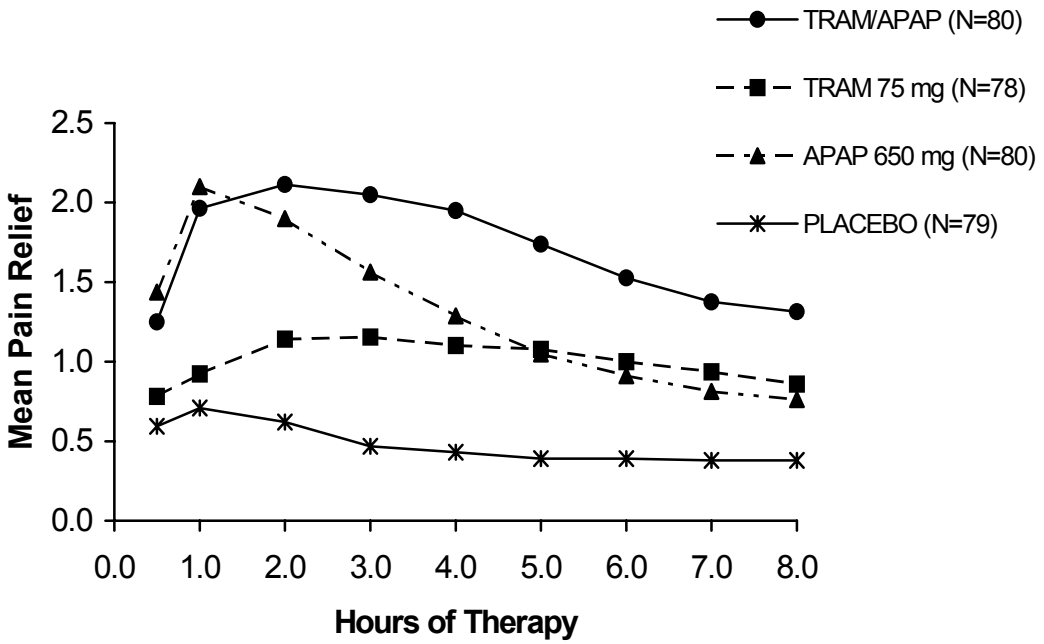
2.5.2 Efficacy and Safety of an Acetaminophen Combination Product

Three single-dose dental pain studies [RW Johnson 1999a, 1999b, 1999c] that included subjects with multiple molar impactions demonstrated the analgesic efficacy of the combination product in the treatment of moderate to moderately-severe pain. In each of these trials, tramadol/acetaminophen was statistically superior to placebo and to each component alone for the three summary efficacy variables: areas under the curve of pain relief against time, of pain intensity difference against time, and of pain relief plus pain intensity difference against time at the 0 to 8 hour interval. Figure 2-4 displays the mean pain relief scores from one of the single-dose oral surgery pain studies and demonstrates the added effectiveness of the tramadol/acetaminophen combination. The time course of activity for tramadol/acetaminophen can be described by a rapid onset and steady rise in

pain relief to peak effect, generally within two to three hours, followed by prolonged analgesic activity (pain relief persists throughout dosing interval). This pattern is clearly a composite of the time-effect curves associated with each of the components in the combination.

The tramadol/acetaminophen combination was well tolerated in subjects with acute pain and had an adverse event profile that was consistent with the known side effects of the individual components. There were no clinically meaningful changes in clinical laboratory tests, vital signs, or physical examination findings.

Figure 2-4. Mean Hourly Pain Relief Scores[8] Demonstrating Added Efficacy of the Tramadol/Acetaminophen Combination



Examination of all available information indicates that the combination of tramadol and acetaminophen is a superior treatment for acute pain because its complementary modes of action provide rapid and long-lasting pain relief, with an excellent safety profile. Furthermore, the concurrent administration of tramadol and acetaminophen in a single,

[8] Pain relief rating scale: 0=none; 1=a little; 2=some; 3=a lot; 4=complete. Displayed scores based on last observation carried forward analysis.

fixed-dose combination tablet facilitates patient compliance, particularly where repeated dosing is necessary.

Within the construct of the WHO Analgesic Ladder [WHO 1996; Sorge 2000], Ultracet™ is well suited as a Step II agent, where the use of a weak opioid analgesic in combination with an adjuvant or non-opioid analgesic is recommended for moderate pain. Therefore, the significant advantage offered by this combination is that it spares the use of strong opioids. The tramadol/acetaminophen combination offers several advantages over tramadol alone, including a faster onset of analgesic activity, greater effectiveness in the treatment of moderate to severe pain, and improved tolerability. The advantages of tramadol/acetaminophen over acetaminophen alone include longer duration of analgesic effect and enhanced relief of moderate to severe pain. This incremental benefit of the combination product over its individual components is relevant for a single dose or for each dose of a repeated, as needed dosing regimen in the relief of pain.

2.6 Conclusions

The data provided in this section demonstrate that the optimal effective and safe adult analgesic dosing schedule of acetaminophen is 1000 mg every four to six hours, up to 4000 mg per 24 hours.

- Results from a recent acute pain dose-response study, individual clinical trials and a systematic review and meta-analysis demonstrate significantly superior efficacy of acetaminophen 1000 mg over lower doses (500 mg and 650 mg). No apparent increase in analgesic benefit of acetaminophen 2000 mg compared to acetaminophen 1000 mg was demonstrated in a single-dose, placebo-controlled dental pain study

- Pharmacokinetic-pharmacodynamic modeling predicts that plasma concentrations following a 1000-mg dose of acetaminophen are consistently at or above the EC_{50} needed for optimal pain relief. Although development of the model was not based on a 650-mg dose of acetaminophen, plasma concentrations of a 650-mg dose of acetaminophen consistently fall below the EC_{50}.

- Controlled clinical trials of acetaminophen 4000 mg per day taken for multiple days or weeks consistently demonstrate efficacy with a good safety profile.

Any reduction in the currently approved single or daily acetaminophen dose would decrease effectiveness and encourage consumers to disregard labeled dosages or switch to alternative analgesics with consequent public health implications (see Section 2.4, Implication of Modifying Acetaminophen Dosing Regimen). Acetaminophen in prescription combination medications provides added effectiveness over the individual components given separately.

3 ACETAMINOPHEN PHARMACOLOGY AND TOXICOLOGY

KEY POINTS

- Acetaminophen pharmacokinetics, which have been thoroughly characterized by prospective well-controlled studies, are consistent and predictable over a wide range of single doses. Therefore, the amount of acetaminophen in the body (and plausible corresponding doses) can be reliably estimated from a plasma concentration(s) measured at a known time following acute acetaminophen ingestion.

- Prospective pharmacokinetic studies show that with repeat doses of 1 and 1.5 g (4 and 6 g/day) acetaminophen plasma concentrations reach steady-state levels within 10 to 15 hours and do not accumulate to higher levels with continued dosing. These results are consistent with the short elimination half-life of two to three hours for acetaminophen and the recommended dosing interval of four to six hours.

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

- The oxidative intermediate, NAPQI, which is mainly generated by CYP2E1 oxidation, is not measurable due to its high reactivity and *instantaneous conjugation with glutathione*. NAPQI may potentially cause hepatotoxicity after a substantial acute overdose; however, glutathione is present in sufficient quantities to conjugate the small amount of NAPQI following therapeutic acetaminophen doses. Additionally, the body continuously replenishes glutathione. As a result, liver toxicity does not occur at normal therapeutic doses.

- With repeat doses of 0.65 and 1 g acetaminophen every six hours, steady-state concentrations of the glucuronide conjugate are higher, and those for the sulfate, cysteine, and mercapurate conjugates are all lower than what would be predicted from single dose data. These findings indicate time-dependent changes in acetaminophen metabolism during repeat dosing, which may reflect up- and/or down-regulation of the different enzymatic pathways.

3.1 Acetaminophen Mechanism of Action

Acetaminophen is both an analgesic and antipyretic drug with weak anti-inflammatory properties. Although the precise mechanism of action is not totally understood, recent work by Boutaud et al [2002] suggests acetaminophen is an inhibitor of the peroxidase portion of cyclooxygenase (prostaglandin H synthase inhibitor). Depending on the redox state and substrate concentrations surrounding the enzymes, acetaminophen may or may not have a significant inhibitory effect. This accounts for its selective activity on pain and fever with little anti-inflammatory effect [Ouellet 2001]. These findings do not exclude the possibility that acetaminophen exerts some effect on pain and fever other than through its effect on prostaglandin H synthase.

Assessment of pain threshold of flexion reflex is generally accepted as an appropriate index of central pain modulation in human subjects [Willer 1977; Willer 1983]. The pain threshold may be assessed by both a visual analog scale and the nociceptive flexion reflex. In response to transcutaneous electrical stimulation, the pain threshold in healthy subjects was significantly raised by 1000 mg intravenous acetaminophen [Piletta 1991]. Additional studies in healthy adults indicate a dose-response relationship and a close association between the subjective and objective pain measures and the area under the concentration-time curves for 500, 1000, and 2000 mg of acetaminophen [Desmeules 1995; Piguet 1998].

Acetaminophen reduces fever by blocking the formation and release of prostaglandins at the hypothalamic thermoregulatory centers [Milton 1976]. A cyclooxygenase-3 enzyme located in the brain has been recently hypothesized to be the target for the analgesic and antipyretic effects of acetaminophen [Botting 2000; Simmons 1999; Simmons 2000]. However, these findings may be accounted for by the action on the peroxidase portion of cyclooxygenases [Ouellet 2001]. Acetaminophen exerts its analgesic and antipyretic effects in the brain in which peroxide levels are not high; whereas, acetaminophen is not anti-inflammatory because peroxide levels are elevated in peripheral tissues.

3.2 Acetaminophen Metabolism

Acetaminophen is primarily metabolized by the liver via three major parallel pathways: glucuronidation, sulfation, and oxidation [Miners 1983; Slattery 1989; Lee 1992; Miners 1992]. Both the glucuronic and oxidative pathways adhere to a first-order rate process,

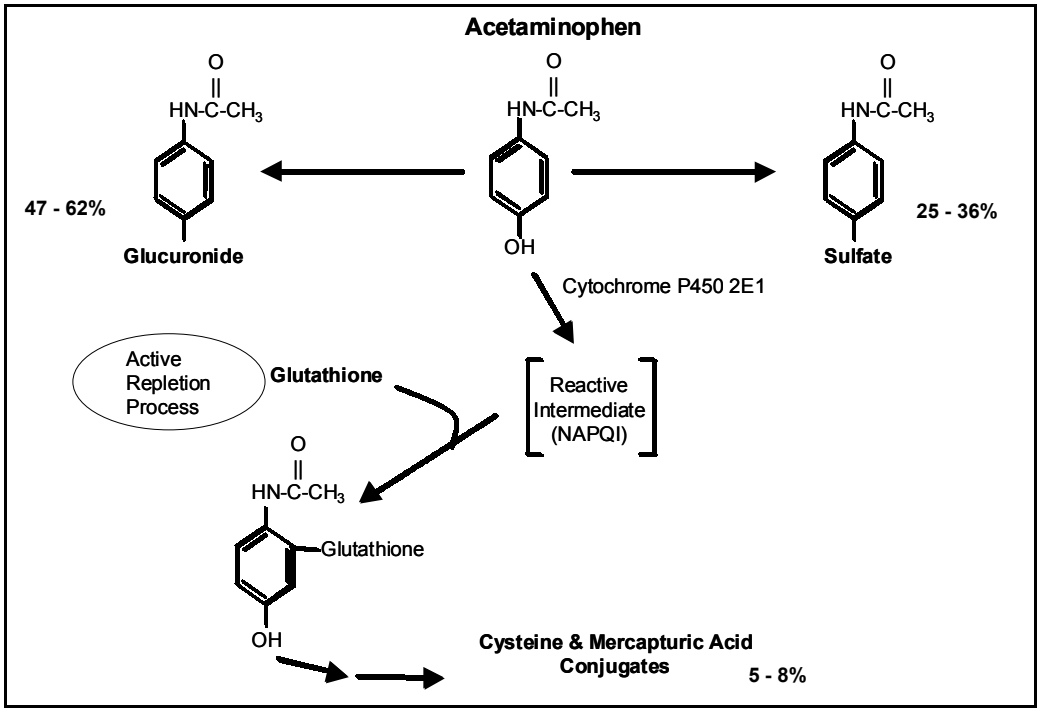
which means the concentration of acetaminophen metabolized increases as the concentration in the liver increases. The sulfate pathway adheres to Michaelis-Menten kinetics, which means the concentration of acetaminophen metabolized remains constant once the concentration in the liver increases above a saturation level.

A schematic of acetaminophen metabolism is shown in Figure 3-1. Less than 9% of a therapeutic dose is excreted unchanged in the urine [Miners 1992]. The major metabolic pathway is glucuronidation, where 47% to 62% of the acetaminophen dose conjugates with glucuronide. These glucuronide conjugates are inactive and nontoxic [Koch-Weser 1976], and are secreted in bile and eliminated in the urine. Glucuronide conjugation is catalyzed primarily by one isoform of glucuronyltransferase (UGT1A6) [Court 2001] with uridine 5'-diphosphoglucuronic acid as an essential cofactor.

The second major pathway of acetaminophen metabolism is sulfation, where 25% to 36% of the dose conjugates with sulfate. These sulfate ester conjugates are also inactive and nontoxic [Koch-Weser 1976], and are readily excreted in the urine. Sulfation is mediated by sulfotransferases, which are heterogeneous cytosolic enzymes, and 3'-phosphoadenosine 5'-phosphate is a cofactor. Sulfotransferase activity rather than sulfate depletion is the rate-controlling factor of acetaminophen sulfation [Blackledge 1991].

The third pathway is oxidation, where 5% to 8% of the acetaminophen dose is metabolized via the cytochrome P-450 enzyme system. The cytochrome P-450 isoenzyme that is primarily responsible for acetaminophen metabolism is CYP2E1 [Manyike 2000]. When acetaminophen is metabolized by CYP2E1, it forms a highly reactive intermediate, N-acetyl-p-benzoquinoneimine (NAPQI). Because NAPQI is highly reactive, it cannot be measured outside the liver nor can it accumulate. This intermediate is rapidly inactivated by hepatocellular stores of glutathione to form cysteine and mercapturate conjugates, which are both inactive and nontoxic [Koch-Weser 1976]. These conjugates are excreted in the urine [Mitchell 1974].

Figure 3-1. Acetaminophen Metabolism



3.3 Acetaminophen Pharmacokinetics

3.3.1 Overview

The pharmacokinetics of acetaminophen have been thoroughly characterized, and are supported by data from numerous prospective, well-controlled studies reported in the literature for children (19 studies), healthy adults (over 40 studies), elderly (11 studies), pregnant women (1 study), renal-impaired adults (6 studies), and hepatic-impaired children (2 studies) and adults (8 studies). Pharmacokinetic results for special populations, including potential drug interactions, are reviewed in Section 4, Assessment of Acetaminophen Safety, within the context of clinical use and safety. Results from studies primarily in healthy adults are summarized in this section to provide the basic principles for understanding acetaminophen's single- and multiple-dose pharmacokinetics.

3.3.2 Single-Dose Pharmacokinetics at Recommended Therapeutic Doses

Oral acetaminophen is rapidly and completely absorbed by passive diffusion from the small intestine. Peak plasma concentrations occur within 0.4 to 1 hour, depending on the product

formulation. Although high-fat foods delay the time to peak concentration for up to an hour [Wessels 1992], the dose is completely absorbed.

Mean peak concentrations of acetaminophen reported for a 650-mg dose range from 6 to 12 μg/mL, and for a 1000-mg dose from 17 to 24 μg/mL. Generally, the maximum concentration of most drugs is inversely related to body weight for a given dose. Thus, for a 110-lb person, 1000 mg acetaminophen corresponds to 13 mg/kg and a higher peak, whereas the same dose for a 165-lb person corresponds to 8.7 mg/kg and a lower peak.

Acetaminophen is uniformly distributed throughout most body fluids, but not in fatty tissue. As a result, the volume of distribution in adults ranges between 0.8 and 1.0 L/kg [Forrest 1982; Ameer 1983]. Because acetaminophen has low protein binding in plasma of only 10% to 25% [Levy 1981; Milligan 1994], it does not compete with drugs that are highly protein bound.

Acetaminophen undergoes first-order elimination from the body, and has a short plasma half-life (t½) that ranges from 2 to 3 hours in healthy young and elderly adults[9] and from 1.5 to 2.9 hours in children[10]. Elimination is only slightly longer in neonates (2.8 to 3.5 hours) [Levy 1975; Hopkins 1990; Autret 1993], the frail elderly (3.4 and 3.8 hours) [Ellmers 1990; Wynne 1990], and patients with mild-to-moderate liver disease (2.2 to 3.4 hours) [Forrest 1979; Benson 1983; Jorup-Ronstrom 1986]. Because acetaminophen clears rapidly from the body, it requires dosing every four to six hours in order to maintain therapeutic levels. Because of its rapid clearance, repeated doses do not lead to accumulation of acetaminophen plasma concentrations [McNeil 1992].

[9] Triggs [1975], Briant [1976], Divoll [1982a,b,c], Bedjaoui [1984], Miners [1988], Bannwarth [1992]

[10] Nahata [1984], Walson [1989], Brown [1992], Kelley [1992], Romsing [2001]

3.3.3 Single-Dose Pharmacokinetics up to Nine Grams

Acetaminophen pharmacokinetics in excess of the recommended therapeutic single doses[11] of 0.65 and 1 g have been studied. Researchers conducting the studies[12] intended to simulate acute overdoses using single doses from 2.8 to 9.1 g within a well-controlled study environment in order to assess differences in absorption between dosage forms [Stork 1996; Douglas 1996] and with various overdose interventions [Rose 1991; Vance 1992; Hassig 1993; Green 2001; Christophersen 2002]. Only pharmacokinetic results for the control groups without absorption interventions (eg, activated charcoal and lavage) are highlighted in this section, because they provide information about those instances when a consumer or patient takes more than a 1 g dose of acetaminophen.

Differences in acetaminophen absorption between immediate-release and extended-release caplets were assessed in two studies of healthy men and women, who received 75 mg/kg (3.8 to 7.2 g, and 4.2 to 7.8 g) as a single acute dose [Stork 1996; Douglas 1996]. In both studies, the supratherapeutic doses were well tolerated, and adverse events (nausea, headache, and light-headedness) were minor and transient. In another study, single doses of 5 g were administered to healthy adults on four occasions, three of which included coadministration of activated charcoal as an intervention [Rose 1991], and they were well tolerated. Similar studies using single-doses of 3.6 or 4 g acetaminophen on four occasions were also reported. Changes in absorption were determined when activated charcoal, without [Green 2001] and with lavage [Hassig 1993; Christophersen 2002], was coadministered with the dose.

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 [Vance 1992]. 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 repeated exposures above the recommended dose were well tolerated, with no adverse events or discontinuations reported.

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

[12] Acetaminophen doses evaluated in the pharmacokinetics studies 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.

The collective pool of 80 subjects in the above crossover 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 coadministration with activated charcoal. All doses were well tolerated, and no patterns in the pharmacokinetic curves indicative of significant metabolic saturation at these doses were found.

Mean pharmacokinetic data for the control groups in the studies are summarized in Table 3-1. Acetaminophen pharmacokinetics at supratherapeutic doses are similar to those at recommended doses. Additionally, peak acetaminophen concentrations and t½ are consistent with linear pharmacokinetics and are, therefore, predictable within this range of supratherapeutic single doses.

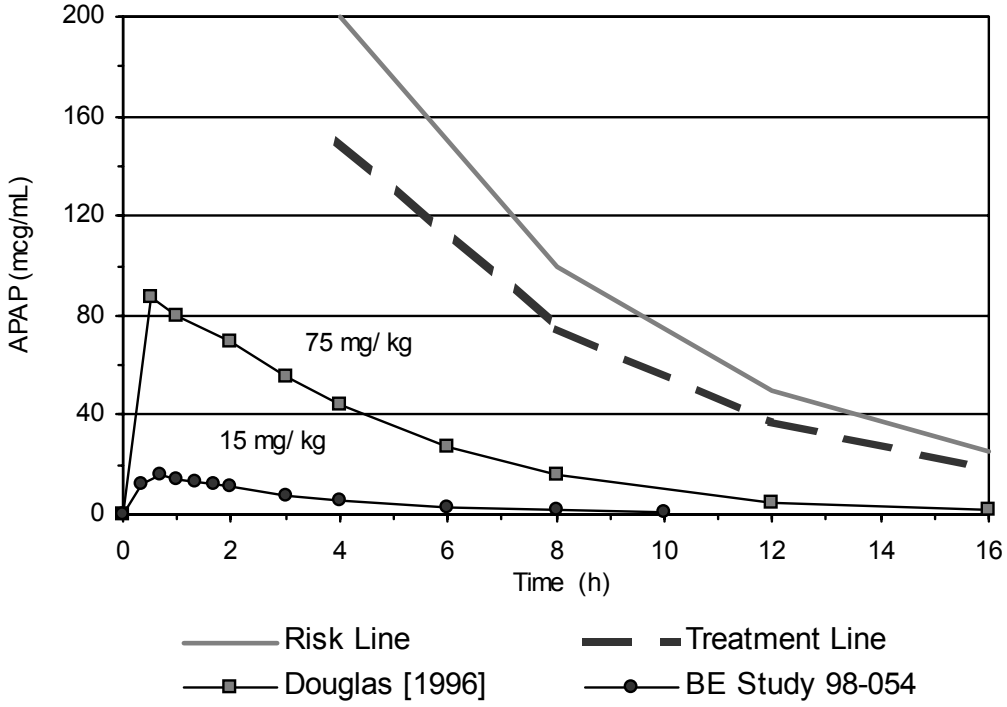
Table 3-1. Mean (sd) Pharmacokinetics Data for Doses Up to Nine Grams

Citation	Study Description	Gender M / F	Weight (kg)	Dose (g) (Range)	AUC_{INF} (μg·h/mL)	C_{MAX} (μg/mL)	T_{MAX} (h)	t½ (h)
Christophersen [2002]	Control[a] vs Charcoal/ Lavage	5 / 7	71.8	3.6[b] 2.8 to 5.3	190	42	1.7	2.2
Green [2001]	Control[a] vs Charcoal	7 / 3	77.4	4.0 (na)	221 (54)	66 (27)	--	2.3 (0.6)
Hassig [1993]	Control[a] vs Charcoal/ Lavage	12	--	4.0 (na)	--	70 (7.4)	--	--
Rose [1991]	Control[a] vs Charcoal	10 / 0	73	5.0 (na)	347 (73)	64 (14)	1.4 (0.52)	2.6 (0.3)
Douglas [1996]	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)
Stork [1996]	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)
Vance [1992]	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 3-2 depicts the mean pharmacokinetic profiles for the 5.6 g (75 mg/kg) acetaminophen dose [Douglas 1996] and the recommended therapeutic dose of 1 g (15 mg/kg) [McNeil 98-054]. This is drawn relative to the risk line for hepatotoxicity and treatment line of the nomogram used to manage acute overdoses. The mean plasma concentrations for this supratherapeutic dose are well below the risk and treatment lines of the nomogram at all times during the study, which further support the safety findings.

Figure 3-2. Mean Data for a Standard (1 g, 15 mg/kg) and Higher (5.6 g, 75 mg/kg) Dose Relative to Risk and Treatment Lines of the Acetaminophen Nomogram



3.3.4 Single-Dose Pharmacokinetics at Very High Doses

A phase I study [Kobrinsky 1996] provided prospective data on the pharmacokinetics of acetaminophen at very high, potentially toxic doses. Nineteen patients with advanced cancer were given high doses (154 to 1007 mg/kg) of acetaminophen chemotherapy followed eight hours later by an intravenous N-acetylcysteine[13] (NAC) regimen. It was anticipated that very high doses of acetaminophen would cause toxicity, but that the coadministration of NAC would selectively protect normal cells versus malignant cells from the toxic effects. Minimal-to-no liver damage occurred in these patients, even when the acetaminophen-NAC regimens were given on more than one occasion. This reaffirms that acetaminophen toxicity does not occur when NAC is administered on a timely basis, despite the very high, potentially toxic doses.

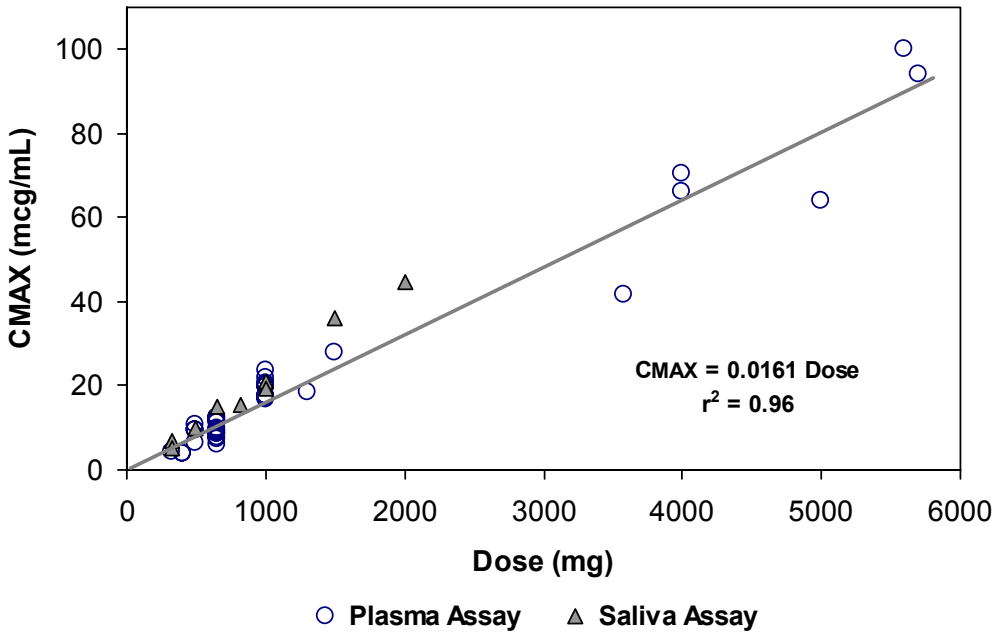
[13] During the 1980s, N-acetylcysteine (NAC) was developed and then approved by FDA as an effective treatment for substantial acute acetaminophen overdose. NAC works by interacting with the toxic intermediate metabolite, NAPQI. The trade name for commercial NAC is Mucomyst.

Serum acetaminophen concentrations from 60 nonvomited courses of therapy in the cancer patients were available to determine distribution volume (0.87 ± 0.31 L/kg) and oral clearance (0.21 ± 0.10 L/kg•h). The mean t½ of 3.6 ± 1.4 h was determined with data from 71 courses of therapy. These pharmacokinetic results at very high doses are similar to those reported in healthy adults for single doses up to six grams.

3.3.5 Relationship of Dose to Pharmacokinetics

Acetaminophen pharmacokinetics have been studied over a wide range of single doses, and are consistent and predictable for half-life, time to peak concentration, and distribution volume. Furthermore, the peak or maximum concentration (CMAX) is linearly related to dose within this range, which is illustrated in Figure 3-3 with data from several published single-dose studies[14]. This means that the peak concentration increases proportionally with increasing dose.

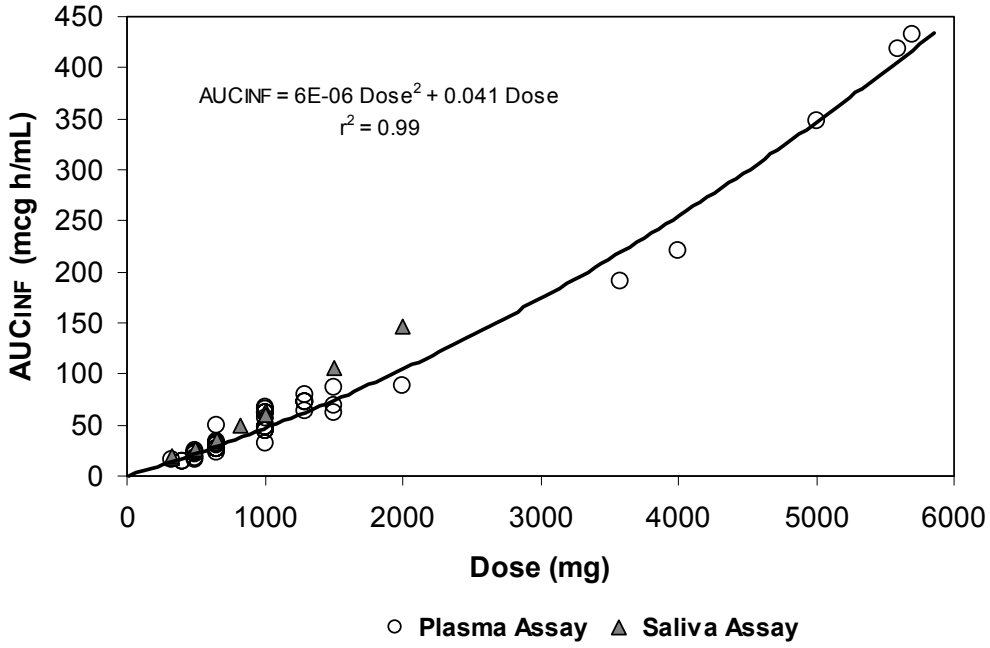
Figure 3-3. Linear-Dose Relationship of Study Mean CMAX Up to Six Grams



[14] Bedjaoui [1984], Rawlins [1977], Ameer [1983], Divoll [1982a,b,c], Hindmarsh [1991], Grattan [2000], Jorup-Ronstrom [1986], Kohli [1982], Miners [1988], Parier [1988], Yiamouyiannis [1994], Mitchell [1983], Borin [1989], Sajahawalla [1991], Douglas [1996], Stork [1996], Christophersen [2002], Green [2001].

The apparent bioavailability of acetaminophen increases slightly with dose due to the saturation of first-pass metabolism [Rawlins 1977], which includes presystemic metabolism in the gastrointestinal epithelium. Figure 3-4 contains mean values for the area under the curve (AUC_{INF}) by dose level from the published single-dose studies described above. The nonlinear increase in the amount of acetaminophen absorbed for doses ranging from 325 to 5700 mg reflects saturation of first-pass metabolism.

Figure 3-4. Nonlinear-Dose Relationship of Study Mean AUC_{INF} Up to Six Grams



3.3.6 Repeat- or Multiple-Dose Pharmacokinetics at 4 and 6 g/Day

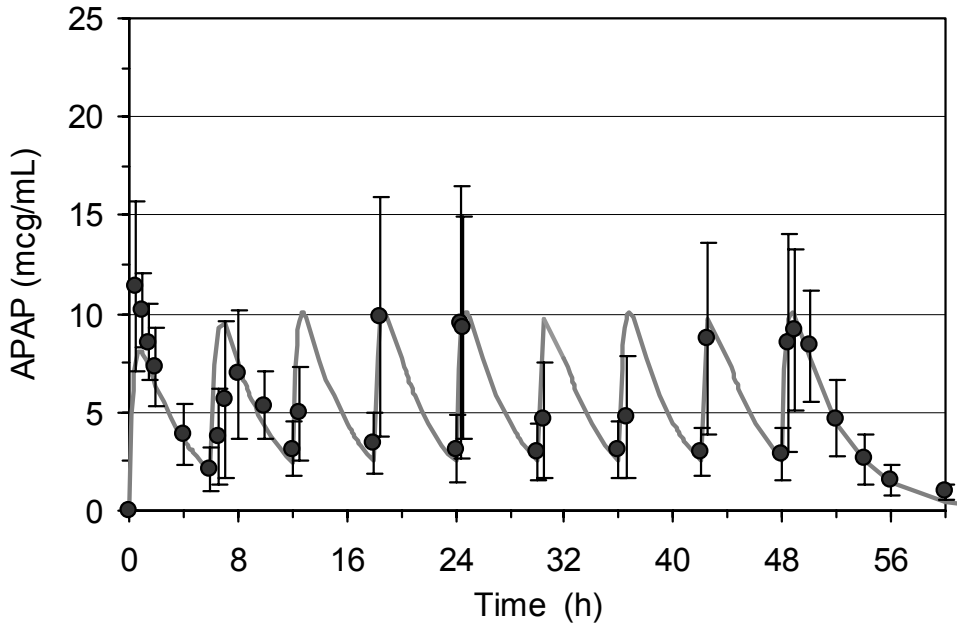
The multiple-dose pharmacokinetics of acetaminophen have been studied at 4 and 6 g daily in healthy adults [Sajahawalla 1991; McNeil 1992; McNeil 2002] and at 4 g daily in hepatic-impaired adults [Benson 1983]. Multiple-dose studies permit further assessment of pharmacokinetic linearity and determination of chronic or time-dependent drug effects, such as enzyme self-induction or unusual accumulation. Drugs with linear pharmacokinetics generally reach steady-state plasma concentrations or are eliminated from the body after five half-lives (t½). Therefore, acetaminophen with a t½ of two to three hours achieves steady-state plasma concentrations after only 10 to 15 hours of repeat dosing. Additionally,

the short t½ and recommended dosing interval of four to six hours results in minimal acetaminophen accumulation between doses.

In one study of healthy adults [Sajahawalla 1991], acetaminophen pharmacokinetics for five doses were determined in saliva samples for 325, 650, 825, and 1000 mg doses administered every six hours. Acetaminophen concentrations in saliva are reported to be virtually equivalent to those in serum. The multiple-dose pharmacokinetic profiles were consistent with drugs that show minimal accumulation due to a short t½. Specifically, mean maximum concentrations at steady state ($C_{MAX,SS}$) for each dose level differed by only 1 to 2 μg/mL from the initial dose.

In a study of healthy subjects [McNeil 1992], plasma acetaminophen concentrations were determined after repeated doses of 1000 mg every six hours for two days (4 g / day), and they are shown in Figure 3-5. As predicted by acetaminophen's short t½ and the dosing interval, there is minimal accumulation and acetaminophen is almost completely eliminated from the plasma at 12 hours following the last dose. The mean $C_{MAX,SS}$ at steady state with repeat doses of 1000 mg every six hours is 11.4 ± 3.8 μg/mL.

Figure 3-5. Repeat-Dose Profile for 1000 mg Every Six Hours (4 g / day) in Healthy Subjects [McNeil 1992]



The multiple-dose pharmacokinetics of acetaminophen were also determined in adults with stable chronic liver disease [Benson 1983]. Safety was assessed by monitoring for adverse events and/or the deterioration of laboratory liver function tests. The dose regimens of 4 g per day for five days during a pilot study with six subjects and for 13 days during the full study with 20 subjects were well tolerated, with no clinical or laboratory adverse event related to acetaminophen observed. The mean t½ of 3.4 hours (2.1 to 5.8 hours) for the hepatic-impaired adults is consistent with the lack of evidence of acetaminophen accumulation noted by Benson [1983].

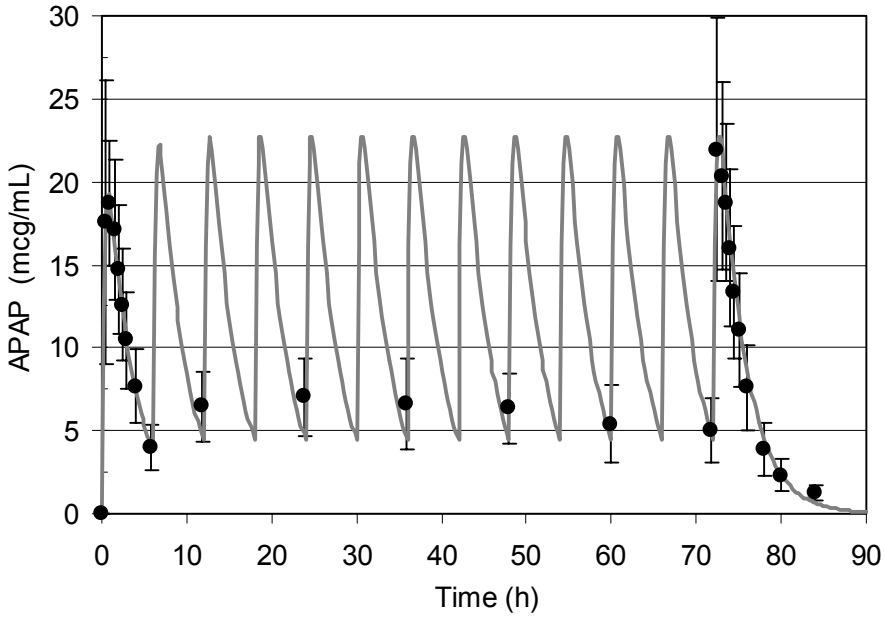
In a recent placebo-controlled study [McNeil 2002], the tolerability and multiple-dose pharmacokinetics and metabolic profile of 4 and 6 g per day, dosed as 1 and 1.5 g acetaminophen every six hours for three days, were determined in healthy adults. Safety was monitored by daily measurements of liver function tests (aspartate aminotransferase - AST and alanine aminotransferase - ALT) during both dosing periods and during a baseline and two washout intervals of three days each. Results of daily liver function tests for subjects taking 4 and 6 g per day of acetaminophen and placebo were all well within normal limits for the duration of the study. Ranges of individual interday variations for both enzymes during the drug administration and washout phases are listed in Table 3-2. They were the same for both groups and reflect the expected day-to-day and time-of-day biological variations in adults.

Table 3-2. Ranges of Subjects' Interday Variation in Liver Function Tests

Study Group	AST	ALT
Acetaminophen (n = 12)	7% to 17%	7% to 25%
Placebo (n = 6)	5% to 17%	6% to 20%

The multiple-dose pharmacokinetic profile for 1.5 g acetaminophen taken every six hours for three days (totaling 6 g/day) is shown in Figure 3-6 and, as predicted from single-dose data and the short elimination t½, steady-state concentrations were reached by the third dose.

Figure 3-6. Repeat-Dose Profile for 1500 mg Every Six Hours (6 g / day) in Four Healthy Subjects [McNeil 2002]



Plasma metabolite concentrations were also measured during the three days of repeat dosing [McNeil 2002]. The data revealed that the formation of glucuronide conjugates increased over time to a higher steady-state level than what would be predicted from glucuronide concentrations following the first dose. In contrast, formation of sulfate conjugates and also the cysteine and mercapturate conjugates decreased over time to lower steady-state plasma concentrations than what would be predicted from the first dose. These results indicate time-dependent changes in acetaminophen metabolism during repeat dosing, which may reflect up- and/or down-regulation of the different enzymatic pathways. The same pattern of change in the rates of metabolite formation (higher glucuronide and lower sulfate) was originally reported by Hendrix-Treacy et al [1986] following repeat doses of 650 mg acetaminophen every six hours for five doses. Moreover, a recent study in mice [Shayiq 1999] demonstrated a down-regulation of CYP2E1 and a potentiated hepatocyte proliferative response with repeat doses of acetaminophen over nine days, which led to protection against a subsequent challenge with a lethal acetaminophen dose in the same mice.

These study results do not support the hypothesis that recurrent or chronic dosing with acetaminophen at ≥5 g / day would be expected to result in hepatic toxicity.

3.4 Acetaminophen Toxicology

3.4.1 Pharmacodynamics of Toxicity

Following acute ingestion of very high acetaminophen doses, there is clinical evidence that *glucuronidation of acetaminophen is not readily saturated*, even among those who have taken massive overdoses [Prescott 1983; 1984]. The fractional urinary excretion of glucuronide metabolites reported in the literature ranges from 47% to 62% for therapeutic doses and from 41% to 75% for very high doses (above 137 mg/kg) [Davis 1976, Prescott 1980]. By contrast, *sulfate conjugation is capacity-limited at very high doses* [Slattery 1979] as evidenced by a decrease in the fractional urinary excretion of sulfate metabolites. The excretion ranges from 25% to 36% for therapeutic doses and from 9% to 16% for very high doses (above 137 mg/kg) [Davis 1976; Prescott 1980].

Only the sulfation pathway is saturated following a substantial acute acetaminophen overdose and, as a result, the fraction of dose metabolized by both the predominant glucuronide pathway and the oxidative CYP2E1 pathway increases. More of the oxidative intermediate, NAPQI, is generated, which conjugates instantaneously with glutathione to produce more inactive cysteine and mercapturate metabolites. NAPQI has the potential to cause hepatotoxicity after a substantial acute overdose if the rate of glutathione consumption by NAPQI exceeds the rate of glutathione synthesis so that the amount of glutathione available in the liver becomes insufficient to conjugate with and detoxify NAPQI.

If NAPQI is not inactivated by glutathione under these specific conditions, it can cause hepatotoxicity by binding with proteins in hepatocytes [Mitchell 1973]. The exact mechanism of liver cell damage is not known, but it is a threshold effect, signaled by a significant rise in serum aminotransferase values. Liver dysfunction occurs with increasing hepatocellular necrosis and, in severe overdose cases without the use of N-acetylcysteine (NAC) treatment, acute centrilobular liver failure can result.

Data analyses demonstrate that hepatic glutathione is present in sufficient quantities to conjugate the small amount of NAPQI that is generated by CYP2E1 oxidation following therapeutic acetaminophen doses [Rumack 2002]. Additionally, the body continuously replenishes hepatic glutathione at an estimated rate of 1.62 mmol/h for a 70 kg person [Lauterburg 1987]. As a result, liver toxicity does not occur at normal therapeutic doses.

3.4.2 Estimation of the Acute Hepatotoxic Dose of Acetaminophen

The actual rates of consumption and synthesis of hepatic glutathione in response to the interaction of glutathione with NAPQI have not been determined in humans. Theoretical estimates that about 70% to 90% of hepatic glutathione stores need to be consumed to cause hepatotoxicity in humans following an *acute dose* were originally extrapolated from mice and hamster *acute dose* data [Mitchell 1973]. In a study of adults, Mitchell et al [1974] determined that the amount of glutathione conjugates formed with 900, 1200, and 1800 mg doses of radiolabeled acetaminophen was 4%, and used these data to estimate the threshold acute dose of hepatotoxicity. 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 liver injury in humans. Therefore, the amount of acetaminophen estimated to generate this much NAPQI[15] is 15 g taken all at once: (4 mmol)(acetaminophen 151.2 mg/mmol) / 4%.

The theoretical estimate of 15 g acetaminophen for the acute hepatotoxic dose in humans by Mitchell et al [1974] 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 the 300 mg/kg acetaminophen [Mitchell 1973]. A study in adults by Lauterburg and Mitchell [Lauterburg 1987] showed that single doses up to 1200 mg acetaminophen stimulate the turnover of cysteine and glutathione. The researchers estimate that the hepatic production of glutathione in humans is approximately 1.62 mmol/h for a liver weight of 1500 g. 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 for a 70 kg person (and 15 g for a 50 kg person). These theoretical estimates are comparable to those estimated by Prescott [1983] from clinical overdose outcomes.

[15] Mitchell et al [1974] rounded the amount of NAPQI generated from 4.2 to 4 mmol in their calculations (70% of 6 mmol equals 4.2 mmol). In a recent review article by Rumack [2002], 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.

Prescott [1983] estimated the threshold acetaminophen dose for hepatotoxicity from a collection of overdose cases in which patients were cared for using supportive therapy. He estimated the amount of acetaminophen absorbed by multiplying the plasma acetaminophen measured at three hours after ingestion with the volume of distribution (0.8L/kg) and paired the doses with 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.

3.4.3 Development of the Nomogram to Manage Acute Overdose Treatment

Current understanding of acetaminophen pharmacokinetics at very high, toxic doses is based mainly on case reports and case series of substantial acute overdoses. The acetaminophen overdose nomogram was developed by Rumack and Matthew [Rumack 1975] by plotting data from 30 previously published cases [Prescott 1971] and an additional 34 unpublished cases. Investigators plotted the line that best discriminated between patients who subsequently showed hepatotoxicity (defined as aspartate aminotransferase levels above 1000 IU) at any time during hospitalization and those who did not [Rumack 2002]. The resulting overdose risk line began at four hours after acute ingestion at 200 μg/mL and intersected 50 μg/mL at 12 hours. The slope of the line happened to represent a 4-h half-life, and was not based on acetaminophen pharmacokinetics [Rumack 2002].

N-acetylcysteine (NAC) is used clinically to treat acute acetaminophen overdose, and acts by interacting with the oxidative intermediate, NAPQI. During the development of NAC in the early 1980s, the treatment line, which was drawn 25% below the original line, was added to conservatively manage the acute overdose cases. This line connects the level of 150 μg/mL at four hours with 37.5 μg/mL at 12 hours. The nomogram is used to estimate the likelihood that a plasma concentration relative to the time postingestion will result in hepatotoxicity and, therefore, whether NAC therapy should be administered.

Smilkstein et al [1988] published a national multicenter study on the efficacy of NAC in which a risk analysis nomogram was used in the analysis. In addition to the original Rumack-Matthew nomogram line and the treatment line (25% lower), this risk analysis nomogram included a third line (50 % higher) that began at four hours after acute ingestion of acetaminophen at 300 μg/mL. This third line was considered the lower limit for high risk of hepatotoxicity due to substantial acute acetaminophen overdose [Smilkstein 1988].

The amount of acetaminophen present in a person (body burden) at a specific time after a substantial acute overdose can also be estimated from a single measurement of plasma concentration and the distribution volume (0.8 to 1 L/kg in adults). Using the following equation based on the fundamentals of pharmacokinetics, body burden at a given time after ingestion may be calculated:

$$\text{Amount in Body at Time (t)} = \frac{\text{Plasma Concentration (}\mu\text{g/mL) at Time (t)}}{\text{Distribution Volume (L/kg)}}$$

3.4.4 Hepatotoxic Potential is Less for Divided Doses of Acetaminophen

In considering the appropriate total daily dose of acetaminophen, the hepatotoxic potential needs to be distinguished between the amount taken all at once (or over a short interval such as eight hours) and the amount divided over the whole day (repeat dosing every four to six hours). Based on the body of scientific evidence provided by prospective pharmacokinetic, metabolic, and clinical data, acetaminophen doses over a ten-fold range that are taken all at once are not hepatotoxic. In addition, pharmacokinetic studies of the wide range of doses taken all at once further support safety, because resulting acetaminophen concentrations were well below the probable-risk threshold of 200 μg/mL at four hours postingestion determined for substantial acute overdose (Rumack-Matthew Nomogram).

The body of scientific evidence provided by prospective pharmacokinetic, metabolic, and clinical data, indicates that the hepatotoxic potential would be less for a 12 g acetaminophen dose, for example, when the dose is divided over the whole day than when it is taken all at once. Specifically, plasma concentrations would not reach as high levels for the divided doses. Also, exposure to several repeat doses of acetaminophen appears to down-regulate the oxidative pathway of acetaminophen metabolism in mice [Shayiq 1999] and adults [McNeil 2002], and to up-regulate the predominant glucuronide pathway in adults [McNeil 2002; Hendrix-Treacy 1986]. In addition, because the total daily dose is not taken all at once but rather as divided doses throughout the day, continuous glutathione synthesis provides an additional 1.62 mmol of hepatic glutathione per hour[16] to the pool available for conjugation with the reactive NAPQI intermediate of acetaminophen [Lauterburg 1987].

[16] Estimate for a 70 kg person.

3.5 Summary

The pharmacokinetics of acetaminophen at recommended single and multiple doses have been well characterized. Additionally, the pharmacokinetics of single acute doses up to ten times the recommended level without NAC administration have been described in several studies, and up to 15 to 100 times the recommended level with NAC administration has been reported in one study of patients with cancer. Collectively, these data allow for a substantially complete characterization of potential acute toxic doses, and provide a framework for considering risk levels for repeated supratherapeutic doses of acetaminophen. (See Section 4, Assessment of Acetaminophen Safety.)

4 ASSESSMENT OF ACETAMINOPHEN SAFETY

KEY POINTS

- Consumers will self-treat pain and their selection of OTC analgesics will depend on availability, accessibility, and effectiveness of these products.

- Evaluation of acetaminophen risks, as with evaluation of NSAID risks, should include all doses that may be self-administered given consumer utilization patterns for OTC-available analgesics.

- Acetaminophen, at currently recommended doses, is used safely by adults, pediatric and elderly patients, as well as by patients with chronic renal disease or chronic stable liver disease. Review of metabolism pathways suggests that there is not an increased risk of toxicity at currently recommended doses of acetaminophen.

- The AERS spontaneous reporting system serves as a signal generating system for rare, unexpected adverse events in marketed products. It cannot be used to determine event rates, dose, or intentionality.

- Case reports are the source of serious hepatic events associated with acetaminophen exposure. These reports are observational and therefore cannot be used to establish causality.

- The number of serious reports for acetaminophen products at the FDA is disproportionately large relative to other monograph analgesics because: a) FDA regulations do not require AERS reporting for OTC monograph drug products, and b) McNeil has submitted serious reports for all single-ingredient acetaminophen products and reports of death for acetaminophen combination products, including published literature and fatalities from AAPCC.

- Data from AAPCC, DAWN and liver transplant centers are consistent, and show that intentional suicide is the most frequent reason for adult acetaminophen overdose.

- Pediatric misadministration rarely results in serious outcome. Rare events could be further prevented by permitting dosage information for children under two on the product label.

- If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.

4.1 Use of Recommended Doses in the General Population

Acetaminophen is widely available and used throughout the United States. The TFM for Over-the-Counter Internal Analgesic, Antipyretic, and Antirheumatic Products provides for an "adult acetaminophen dose up to 1000 mg, not to exceed 4000 mg in 24 hours for not more than ten days."

A recent survey of medication use in the United States reported that acetaminophen was used by 23% of adults in the preceding week [Kaufman 2002]. Market data from AC Nielsen Home Scan estimate that 40,250,000 households in the United States bought an OTC single-ingredient adult acetaminophen product during the 12-month period ending June 2002. Over the same time period, an estimated 28,000,000 United States households bought an OTC combination ingredient adult acetaminophen product. Based on data provided by Information Resources, Inc., it is estimated that in 2001 approximately 11 billion tablets of OTC single-ingredient adult acetaminophen were purchased, as well as nine billion tablets of OTC combination-ingredient adult acetaminophen. In regard to prescription products, IMS Health market data report that 155,000,000 prescriptions were filled for acetaminophen-containing prescription analgesic products in the year 2001.

At least 500 published and unpublished controlled clinical trials in adults and children have evaluated acetaminophen for the relief of pain or fever. These studies include single and multiple dose treatments. Most studies were less than 14 days in duration, although the longest study duration was two years. At least 31,500 study participants were exposed to acetaminophen with approximately 1800 subjects exposed for 14 days or more. No significant safety issues were reported in any of these studies. In particular, there have been no published reports of serious renal or hepatic adverse events at therapeutic doses of up to 4000 mg per day in divided doses used for two weeks [McGuiness 1969, Choffray 1987, Lequesne 1997], three weeks [Amadio 1983; Kroner 1991], four weeks [Hickey 1982; Kjaersgaard-Anderson 1990; Bradley 1991], five weeks [Stein 1996], six weeks [Matts 1983; Geba 2002], 12 weeks [Ertuck 1998] or as long as two years [Williams 1993].

Moreover, at recommended doses, acetaminophen has not been shown to increase the risk of developing renal diseases [Prescott 1996; Prescott 1990; Edwards 1971; Rexrode 2001] or upper gastrointestinal ulceration/bleeding [Hoftiezer 1982; Johnson 1981; Peura 1997; Singh 2000; Langman 1994]. This observation is consistent with its minimal inhibitory effect on peripheral prostaglandin synthesis [Jackson 1984] and on gastric prostaglandin synthesis [personal communication Cryer 2002].

In addition to these studies, Lesko and Mitchell [Lesko 1995] enrolled more than 84,000 febrile children in a randomized, double-blind, acetaminophen-controlled trial to assess the risk of rare but serious adverse events following the use of pediatric ibuprofen. Of the children included in the analysis, 28,130 received acetaminophen and none experienced anaphylaxis, or serious hepatic, gastrointestinal or renal effects.

4.2 Use of Recommended Doses in Selected Populations

Some authors have theorized that metabolic or pharmacokinetic alterations in certain populations require a dose reduction of acetaminophen to avoid potential increased risk for toxicity. However, results of well-designed clinical studies indicate that a dose reduction is not necessary for elderly adults, patients with chronic renal disease, adult and pediatric patients with chronic, stable liver disease, and obese adults. Each of these population groups is discussed in the following sections.

4.2.1 Elderly Adults

The pharmacokinetics of acetaminophen have been well characterized in the elderly population. Ten studies included 145 elderly adults, ranging in age from 65 to 92 years, and 97 young adults. As shown in Table 4-1, no differences in the elimination half-life of acetaminophen between young and elderly adults were observed. Two of the studies also included a subgroup of 35 elderly adults who were receiving continuous hospital care for chronic disabling conditions [Ellmers 1990; Wynne 1990]. The mean half-lives reported for these *frail* elderly adults (3.4 and 3.7 h) were only slightly prolonged.

Small differences in acetaminophen clearance were reported in some studies (Table 4-1); however, in a comprehensive metabolic study by Miners et al [1988], the formation clearance of glucuronide and glutathione conjugates were the same in young and elderly adults. This finding provides prospective scientific data that the amount of acetaminophen metabolized via the oxidative pathway, from which the highly reactive intermediate, NAPQI, is generated, does not increase with age. Only the formation clearance of the sulfate conjugates was less in elderly adults [Miners 1988], which may contribute to the slightly lower clearance of acetaminophen.

Table 4-1. Acetaminophen Pharmacokinetics in Elderly Adults (Study Means)

Study Group	Elimination Half-Life (h)	Clearance (mL/min/kg)	References
Elderly Adults (n = 145)	2.7; 2.8; 2.5; 2.2; 2.8; 2.5; 2.6; 2.2; 2.2; 2.7; 2.4	3.7; 3.3; 5.1; 4.2; 3.7; 3.9; 3.4; 5.7; 5.6; 3.7	Bannwarth [2001]; Bedjaoui [1984]; Briant [1976]; Divoll [1982a,b,c]; Triggs [1975]; Miners [1988]; Ellmers [1990]; Wynne [1990]
Young Adults (n = 97)	2.1; 1.8; 2.6; 2.6; 2.7; 1.8; 2.1; 2.1	7.8; 5.7; 4.6; 5.1; 4.1; 6.8; 6.1; 4.7	Bedjaoui [1984]; Briant [1976]; Divoll [1982a,b,c]; Triggs [1975]; Miners [1988]; Wynne [1990]

Recently, Bannwarth et al [2001] evaluated the multiple-dose pharmacokinetics of acetaminophen in elderly adults (89 $\pm$ 4 y). After seven days of repeat dosing, acetaminophen did not accumulate in the plasma, and the elimination half-life (2.8 $\pm$ 0.3 h) was the same as that reported for young adults. In conclusion, acetaminophen is safe for use in the elderly population as currently labeled.

4.2.2 Patients with Renal Disease

Well-controlled, prospective data summarized below indicate that acetaminophen can be used in patients with moderate-to-severe renal failure, with no dosage adjustment. This favorable view on the renal safety profile of acetaminophen is shared also by the National Kidney Foundation, which recommends acetaminophen as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease [Henrich 1996].

Martin and colleagues [Martin 1991] found that patients with chronic renal failure had slightly higher plasma concentrations of inactive glucuronide and sulfate metabolites than healthy subjects during repeated dosing up to ten days. The metabolites rapidly cleared when acetaminophen was discontinued. In patents maintained with hemodialysis [Martin 1993], the same researchers found that plasma acetaminophen metabolites were more rapidly cleared compared to healthy subjects. They concluded that use of recommended doses of acetaminophen was safe in patients with moderate-to-severe renal failure.

Several single-dose studies demonstrate accumulation of acetaminophen metabolites in patients with moderate chronic renal failure and in anephric patients [Lowenthal 1976; Chan 1997; Prescott 1989] for whom hemodialysis appeared to be the major route of elimination [Oie 1975]. However, accumulation of these inactive and nontoxic metabolites has no implications for safety [Lowenthal 1976]. Furthermore, metabolism appears unaltered,

since the percentage of urinary metabolites was similar to that of healthy volunteers [Prescott 1989].

Data demonstrate that there is no risk of acetaminophen toxicity at currently recommended doses in patients with moderate-to-severe renal failure and that a dosage adjustment is unnecessary in this patient population.

4.2.3 Patients with Liver Disease

Slower metabolism of acetaminophen, increased activity of the cytochrome P-450 enzyme system, or depleted glutathione stores are cited as theoretical risk factors for acetaminophen hepatotoxicity in patients with chronic liver disease. However, acetaminophen has been studied in both adults and children with a wide variety of liver diseases including various types of cirrhosis, hepatitis, nodular transformation, congenital hepatic fibrosis, and α_1-antitrypsin deficiency. In none of these conditions is there evidence of an increased risk for hepatotoxicity at currently recommended acetaminophen doses.

Andreasen [1979] evaluated the pharmacokinetics of acetaminophen in patients with and without liver disease. Both a single dose (1000 mg), and five days of acetaminophen (1000 mg three times per day) were studied in patients with biopsy-confirmed cirrhosis. There was no accumulation of acetaminophen during five days of therapy, nor were there any clinical or biochemical signs of hepatotoxicity.

Forrest and associates [Forrest 1979] compared acetaminophen metabolism following a single 1500 mg dose to normal subjects, patients with mild liver disease, and patients with severe liver disease. There were no significant differences between groups in overall 24-hour urinary excretion of acetaminophen and its glucuronide, sulfate, cysteine, and mercapturic acid conjugates, evidence that acetaminophen metabolism was similar to that in normal subjects.

Benson [1983] conducted a double-blind, two-period crossover study of 4000 mg/day of acetaminophen for 13 days in patients with stable chronic liver disease. Acetaminophen did not accumulate and the pharmacokinetics were similar to that reported in healthy subjects.

In a placebo-controlled study [Dargere 2000], French patients with chronic hepatitis C were given three grams of acetaminophen daily or placebo for seven days. Transaminase and

viral loads were unaffected by treatment. The authors concluded that recommended doses of acetaminophen could be used for patients with chronic hepatitis C. [Note: The recommended daily dose of acetaminophen in France at the time this study was conducted was three grams per day. It is now four grams per day.]

A study in patients with acute viral hepatitis (A, B, nonA/nonB) compared the changes in pharmacokinetics of acetaminophen during the acute and recovery phases of the disease [Jorup-Ronstrom 1986]. The mean half-life was 3.2 and 2.1 h for the acute and recovery phases, respectively. Although the elimination rate was slightly prolonged, the researchers conclude that acetaminophen may be given in conventional doses to patients with hepatitis.

Based on results of these studies, acetaminophen may safely be used in adults with existing liver disease at the currently recommended doses, without exacerbation of these underlying conditions.

4.2.4 Pediatric Patients with Liver Disease

Acetaminophen has also been studied in pediatric patients with liver disease (ages seven months to 12 years). Following a single (10 mg/kg) acetaminophen dose, the pharmacokinetic profiles in pediatric patients with mild, moderate, or severe liver disease were not significantly different [al-Obaidy 1996]. In another study [Careddu 1961], acetaminophen elimination of a 10 mg/kg dose by children experiencing an acute phase of infectious hepatitis was determined. The mean half-life of 2.96 h was slightly prolonged compared with 2.24 h for healthy control children. Elimination half-lives in four children were redetermined during the recovery phase, and were found to decrease to control values. Data demonstrate that acetaminophen may be safely used in children with existing liver disease at recommended doses.

4.2.5 Obese Adults

There has been a suggestion that obesity may increase the risk of acetaminophen hepatotoxicity. O'Shea et al [1994] studied the pharmacokinetics of chlorzoxazone (a putative probe for CYP2E1 activity) to evaluate the effect of obesity on CYP2E1 activity. Based on chlorzoxazone urinary metabolite data, the authors concluded that CYP2E1 is induced in obese adults and that this could impact the metabolic pathway of a number of drugs metabolized by CYP2E1, including acetaminophen. None of these other drugs were investigated in this study. However, acetaminophen pharmacokinetic data have been investigated in obese adults [Abernethy 1982]. In this prospective study, 650 mg

acetaminophen was administered intravenously to obese men (297 lb), obese women (193 lb), control men (155 lb), and control women (121 lb). Acetaminophen distribution volume per total body weight was slightly lower in the obese adults but, more importantly, the half-life and metabolic clearance per total body weight did not differ among groups.

4.2.6 Conclusions

Available data demonstrate that the use of recommended acetaminophen doses in the general population does not result in hepatic, gastrointestinal or renal toxicity. Furthermore, patient populations theorized to have impaired metabolism that might put them at special risk for toxicity, such as the elderly, patients with renal or hepatic impairment, pediatric patients with liver disease, and obese patients are not at increased risk of toxicity from acetaminophen. There is no evidence to support the need for a dosage adjustment in these patients.

4.3 Metabolic Alterations Theorized to Increase Risk

Genetic or induced metabolic alterations theoretically might increase the risk for hepatotoxicity with acetaminophen use or overdose. Examples include CYP2E1 or other isoenzyme induction, glucuronidation disorders (UGDP deficiency), or glutathione deficiency or depletion. Available data on each of these are summarized in the following sections, and support the safe use of currently recommended doses of acetaminophen in these situations.

4.3.1 Situations In Which Cytochrome P-450 2E1 Might Be Induced

Approximately 5% to 8% of an acetaminophen dose is metabolized via the cytochrome P-450 isoenzyme, CYP2E1. The contribution of other isoenzymes is negligible [Manyike 2000], so only CYP2E1-inducing drugs have any potential for an interaction with acetaminophen via this pathway. Two agents have been shown in man to induce CYP2E1, long-term alcohol intake and prolonged isoniazid therapy [Omiecinski 1999].

Acute Alcohol Use. Acute alcohol ingestion refers to the occasional or intermittent use of alcohol. The amount of alcohol considered to be an acute ingestion can range from one or two drinks to a weekend “binge.” Binge drinkers have been theorized to be a patient population that may have potential for increased risk of acetaminophen hepatotoxicity. However, when taken together, alcohol competes with acetaminophen for CYP2E1. CYP2E1 accepts alcohol more readily than acetaminophen; therefore, less NAPQI is

produced [Sato 1981; Altomare 1984; Banda 1982]. In the presence of alcohol, it is possible that acetaminophen may be diverted to the glucuronidation and sulfation pathways. Consequently, the overall result is that in the presence of alcohol, a smaller percentage of acetaminophen may be expected to be metabolized to the toxic intermediate (NAPQI) than would otherwise be the case [Rumack 2002].

In a study by Thummel [2000], the fraction of acetaminophen dose presumptively converted to NAPQI (measured as urinary cysteine and mercapturic conjugates) was modestly increased when alcohol was infused over the course of one evening. Nonetheless, this increase was clinically insignificant, and the authors concluded that the maximum recommended dose of acetaminophen (4 grams/day) can be safely consumed by healthy adults after ingestion of alcohol.

Chronic Alcohol Use. Prolonged excessive alcohol use may induce the amount of CYP2E1 [Lieber 1999]. Thus, chronic heavy alcohol abusers might be at increased risk of liver toxicity following excessive acetaminophen use. While some [Makin 2000] have found no correlation between alcohol consumption and the severity of hepatotoxicity following acetaminophen overdose, others suggest that alcoholics may be at increased risk from recommended doses. Available case reports usually involve cases of severe chronic alcoholics and the dosages most often exceed recommended doses or involve substantial overdose [Schiodt 1997; Seeff 1986; Zimmerman 1995]. Even so, these case reports are problematic with regard to drug histories. Chronic alcoholics and drug overdose patients most often cannot provide a reliable history of the medications or amounts they have taken [Broughan 2000; Matsika 1999; Montague 2001; Pohjola-Sintonen 2000].

The only prospective data available [Kuffner 1997, 2001] demonstrate that chronic alcoholics can take recommended doses of acetaminophen (up to four grams per day) without added risk of liver injury. In these prospective, placebo-controlled studies, the researchers evaluated an actively drinking group of alcoholics with a high prevalence of malnourishment. The study participants abruptly stopped their daily alcohol intake and took acetaminophen the next day. This should theoretically make them vulnerable to acetaminophen injury because their CYP2E1 would be maximally induced from the alcohol and there would be no alcohol present in the body to compete with acetaminophen for metabolism by CYP2E1. However, there was no statistically significant difference in mean values for AST, ALT, or International Normalized Ratio for alcoholics given four grams per day of acetaminophen compared to those given placebo. Additionally, the investigators

performed an analysis of the malnourished patients that showed there was no increase in AST or ALT levels in these patients.

Other studies using single acetaminophen doses (up to 20 mg/kg) in chronic alcohol abusers did not show an increase in the production of the mercapturic metabolite [Critchley 1982, 1983; Skinner 1990; Villeneuve 1983]. This finding is additional evidence that chronic alcohol use does not significantly alter acetaminophen metabolism or risk for hepatotoxicity with recommended doses. However, the caution to have anyone who consumes three or more alcoholic drinks every day talk with their doctor before using acetaminophen or other pain relievers remains appropriate, and the need to strongly urge chronic alcoholics not to exceed the recommended dose is very important.

Isoniazid. Isoniazid is primarily metabolized by CYP2E1 [Lieber 1997; Omiecinski 1999] and induces CYP2E1 [Bray 1992; Parkinson 1996; Lieber 1997; Manyike 2000]. Studies in healthy subjects clearly demonstrate that isoniazid blocks the formation of the toxic metabolite, NAPQI, [Epstein 1991; Zand 1993]. Thus, concomitant use of isoniazid is unlikely to potentiate the risk of acetaminophen-induced hepatotoxicity at recommended doses. In fact, it has been postulated, but not demonstrated, that concurrent use of isoniazid may protect against hepatotoxicity in an acute acetaminophen overdose [Epstein 1991; Zand 1993]. The isoniazid induction of CYP2E1 is short-lived, lasting only 12 to 48 hours after the discontinuation of isoniazid [Zand 1993; Chien 1997], so theoretically only during this period would one consider whether there may be potentiation of a substantial acetaminophen overdose.

4.3.2 Concomitant Use of Drugs That Induce Other Cytochrome P-450 Isoenzymes

When evaluating the possibility of a potential interaction between acetaminophen and drugs that induce cytochrome P-450 isoenzymes other than CYP2E1, it is important to remember that only a small amount (5% to 8%) of acetaminophen is metabolized by cytochrome P-450. The CYP2E1 isoenzyme is primarily responsible for the conversion of acetaminophen to NAPQI, whereas CYP3A4 and CYP1A2 play negligible roles, if any, in the metabolism of acetaminophen [Manyike 2000].

Some reports have suggested that patients taking long-term anticonvulsant therapy (eg, phenobarbital, phenytoin, or carbamazepine), who overdose on acetaminophen may be at increased risk for hepatotoxicity as a result of enhanced acetaminophen metabolism due to induction of CYP3A4 and CYP1A2 [Wright 1973; Mitchell 1974; Perucca 1979; Miners

1984; Bray 1992]. Table 4-2 lists the effect of each of these drugs on CYP2E1 and provides a list of the other cytochrome P-450 isoenzymes involved in their metabolism. Additionally, a review of the published medical literature clearly indicates that patients on long-term anticonvulsant therapy are not at increased risk of hepatotoxicity when acetaminophen is taken at recommended therapeutic doses [Kampffmeyer 1969; Kampffmeyer 1971; Neuvonen 1979; Prescott 1981; Makin 1995].

Table 4-2. Effect of Concomitant Use of Drugs That Induce Cytochrome P-450 Isoenzymes

Drug	Effect On CYP2E1	Cytochrome P-450 Isoenzyme(s) Induced	References
Anticonvulsants			
Phenobarbital	None	CYP2B6 CYP2C8, CYP2C9 CYP1A2, CYP3A4	[Parkinson 1996; Chang 1997; Anderson 1998; Omiecinski 1999; Fuhr 2000]
Phenytoin	None	CYP2C9 CYP3A4	[Prescott 1981; Anderson 1998]
Carbamazepine	None	CYP2C9 CYP3A4	[Parkinson 1996; Tomlinson 1996; Anderson 1998]
Other Drugs			
Rifampin	None	CYP3A4 CYP2B6 CYP2C8, CYP2C9, CYP2C19	[Pichard 1990; Parkinson 1996; Chang 1997; Anderson 1998; Lehmann 1998; Thummel 1998; Omiecinski 1999; Fuhr 2000]
Omeprazole	None	CYP1A2	Diaz 1990; Rost 1992; Parkinson 1996; Sarich 1997; Omiecinski 1999]

Other drugs metabolized by CYP1A2 and CYP3A4 include rifampin and omeprazole. Manyike and colleagues [Manyike 2000] found that rifampin pretreatment had no significant effects on the formation of NAPQI or the recovery of thiol metabolites formed by the conjugation of NAPQI with glutathione, suggesting that even when induced, the contribution of CYP3A4 to NAPQI formation is negligible. This study also provided convincing evidence of the predominance of CYP2E1 in NAPQI formation in humans, and suggests that the contribution of CYP3A4 is minor.

Omeprazole has been shown to induce the activity of CYP1A2 in humans [Diaz 1990; Rost 1992; Parkinson 1996; Sarich 1997; Omiecinski 1999]. However, data demonstrate that CYP1A2 induction by omeprazole is not clinically significant, and since CYP1A2 has a negligible role in acetaminophen metabolism, it is unlikely to increase the risk of acetaminophen-induced hepatotoxicity [Xiadong 1994; Sarich 1997].

4.3.3 Situations Affecting Glucuronidation

In humans, the major metabolic pathway of acetaminophen is glucuronidation, accounting for 47% to 62% of a dose [Koch-Weser 1976]. These glucuronide conjugates are inactive and nontoxic (see Section 3.2, Acetaminophen Metabolism). Addressed below are theoretical concerns that decreased glucuronidation capacity may alter the pharmacokinetics of acetaminophen and increase risk of hepatotoxicity.

4.3.4 Fasting and UDP-Glucuronic Acid or Precursor Depletion

Acetaminophen is metabolized to acetaminophen glucuronide by glucuronosyltransferase, with uridine diphosphoglucuronic acid (UDP-GA) as a necessary co-factor. A theoretical concern is that a deficiency in the precursors for UDP-GA may decrease glucuronidation capacity and shift acetaminophen metabolism to other pathways, ie, microsomal oxidation, via CYP2E1. In 1994, Whitcomb and Block published a case series and suggested that hepatotoxicity following acetaminophen overdose is enhanced by fasting [Whitcomb 1994]. Presumptively, fasting depletes precursors for glucuronidation and shifts metabolism to the cytochrome pathway. Although severe caloric restriction can deplete UDP-GA precursors in laboratory animals, no clinical data indicate conclusively that this occurs in humans or that a decrease in glucuronidation would lead to an increase in the microsomal oxidation pathway of acetaminophen metabolism [Price 1988].

Additional studies have evaluated the effect of fasting on acetaminophen disposition. A recent clinical study found that there was no change in urinary metabolites and unaltered liver function tests with use of a single two-gram dose of acetaminophen in obese, fasting caloric-restricted adults [Schenker 2001]. Another study showed no difference in acetaminophen pharmacokinetics between fasting and nonfasting patients [Kohli 1982]. Taken together, these studies indicate that fasting does not lead to decreased glucuronidation that would shift acetaminophen metabolism toward the microsomal oxidation pathway.

4.3.5 Gilbert's Syndrome and UDP-Glucuronosyltransferase Depletion

The primary enzymatic deficiency in Gilbert's is in uridine diphosphoglucuronosyltransferase (UDP-GT) activity, specifically the isoform UGT1A1. This deficiency leads to hyperbilirubinemia [De Morais 1992; Bosma 1995; Radu 2001]. Acetaminophen glucuronidation involves a different UDP-GT isoform, UGT1A6 (and to a lesser extent UGT1A9) [Bock 1993; Court 2001].

Concern has been expressed that glucuronidation is decreased in patients with Gilbert's syndrome, which would lead to more acetaminophen undergoing oxidation by cytochrome P-450, resulting in more NAPQI being formed at therapeutic doses.

Studies of acetaminophen metabolism in patients with Gilbert's syndrome show little or no reduction in glucuronidation capacity for acetaminophen metabolism [Schmid 1959; Ullrich 1987]. Others have shown a slight decrease in glucuronidation capacity accompanied by a modest increase in the proportion of glutathione-derived metabolites, but only in the subset of Gilbert's syndrome patients with less than 50% glucuronidation [Esteban 1999]. This amount of increase in glutathione-derived metabolites is unlikely to have clinical significance.

Court and colleagues [Court 2001] confirmed the results of a previous study [Bock 1993] indicating that UGT1A6 was the primary isoform involved in the glucuronidation of acetaminophen, with UGT1A9 contributing a lesser extent. UGT1A1 contributed to a small extent. In addition, Court also found that UGT1A1 activity varied considerably among human livers, enough to overshadow any changes that might be seen in Gilbert's syndrome.

Available data suggest that UGT1A6, and to a lesser extent, UGT1A9 are the most important isoforms for acetaminophen glucuronidation in humans (not UGT1A1), so there is no support for an increased risk of hepatotoxicity in these patients who take acetaminophen at recommended doses. Additional human data might be informative to determine if there is any risk with higher than recommended single doses (eg, 3- or 4-gram single doses).

4.3.6 Glutathione

Glutathione plays an important role in detoxifying intermediary metabolites of multiple analgesics, namely, NSAIDs, morphine and acetaminophen. It follows that individuals with hepatic glutathione deficiency or with a deficiency in glutathione synthetase (the enzyme responsible for coupling NAPQI with glutathione) may be theorized to be at increased risk for acetaminophen toxicity.

4.3.6.1 Glutathione Synthetase Deficiency

In vitro studies [Spielberg 1981; 1985] on cells from patients with glutathione synthetase deficiency and from heterozygotes for the disorder suggest the possibility of decreased

ability to detoxify the reactive metabolite of acetaminophen. To our knowledge, no one, either heterozygous or homozygous for the deficiency, has taken acetaminophen and thus, there are no reports of in vivo toxicity. Glutathione synthetase deficiency is an extremely rare inborn error of metabolism. In fact, there are under one dozen known pedigrees in the world. These patients are easily identified as they typically have clinical symptoms such as hemolytic anemia, severe acidosis and 5-oxoproline in the urine. Patients with glutathione synthetase deficiency and their parents are routinely instructed by their healthcare provider to avoid acetaminophen-containing products [personal communication Spielberg 2002].

4.3.6.2 Disorders in Which Glutathione Might be Depleted

Glutathione Levels in Alcoholics. Chronic alcoholics have been reported to have decreased intrahepatic glutathione stores [Jewell 1986]. The extent to which glutathione is actually depleted in alcoholics is uncertain. However, as previously reviewed, well-controlled, prospective studies [Kuffner 1997; 2000] demonstrate that therapeutic doses of acetaminophen do not cause liver injury in chronic alcoholics. The impact of this in cases of substantial overdose is not determined.

Use of Acetaminophen in HIV-infected Patients. HIV-infected adults and children appear to show a progressive decrease of glutathione in peripheral blood lymphocytes at different stages of the disease. The degree of correlation between blood and hepatic glutathione is unclear. It has been suggested that drugs that deplete glutathione may make glutathione-deficient individuals more susceptible to toxicity [Herzenberg 1997]. Nevertheless, there are no human data suggesting that acetaminophen depletes total body or plasma glutathione stores, when taken at recommended therapeutic doses in patients infected with HIV.

Use of Acetaminophen in Patients with Hepatitis C. Chronic hepatitis C infection can lead to a decrease in glutathione levels [Lauterburg 2002]. This decrease appears not to alter acetaminophen safety and at least one prospective trial showed that hepatitis C patients can use therapeutic doses of acetaminophen without clinical evidence of liver injury [Dargere 2000].

Use of Acetaminophen in Patients with Cirrhosis of the Liver. Patients who have cirrhosis of the liver reportedly have decreased glutathione levels, possibly resulting from the impaired formation of the precursor amino acid cysteine from methionine [Lauterburg 2002; Rumack 2002]. However, the activity of the CYP2E1 isoenzyme that metabolizes

acetaminophen to NAPQI is also decreased in patients with cirrhosis [Lauterburg 2002; Rumack 2002]. Importantly, prospective data indicate that currently recommended doses of acetaminophen may be used in adults with cirrhosis, and this use will not exacerbate their condition [Benson 1983].

4.3.7 Conclusion

These data support that use of recommended doses of acetaminophen in certain subpopulations believed to have glutathione deficiency provides no increased risk of hepatotoxicity and does not require a dosage adjustment. Additionally, patients with glutathione synthetase deficiency are exceedingly rare, easily identified and should be instructed by their physicians to avoid the use of acetaminophen.

4.4 Clinical Characteristics of Acute Acetaminophen Overdose

Hepatic injury is the principal toxic effect of a substantial acetaminophen overdose. Signs and symptoms of acetaminophen overdose show a consistent pattern, and the clinical course generally occurs in a three-phase sequential pattern. The first phase begins shortly after ingestion of an overdose and lasts for 12 to 24 hours. The patient may manifest signs of gastrointestinal irritability, nausea, vomiting, anorexia, diaphoresis, and pallor. Many patients with early symptoms never progress beyond the first phase and recover without sequela.

If toxicity continues or is to ensue, there is a latent phase of up to 48 hours. During this second phase, initial symptoms abate and the patient may feel better. However, hepatic enzymes, bilirubin, and prothrombin time or International Normalized Ratio values will progressively rise, with hepatic enzymes often rising to striking levels. Right upper quadrant pain may develop as the liver becomes enlarged and tender. Most patients do not progress beyond this phase, especially if given N-acetylcysteine (NAC) treatment early in the course.

Signs and symptoms of the third phase depend on the severity of hepatic damage and usually occur from three to five days following overdose ingestion. Symptoms may be limited to anorexia, nausea, general malaise, and abdominal pain in less severe cases or may progress to confusion, stupor, and sequelae of hepatic necrosis including jaundice, coagulation defects, hypoglycemia, and encephalopathy, as well as renal failure and cardiomyopathy. Death, if it occurs, is generally the result of complications associated with

fulminant hepatic failure. Mortality rates in patients with toxic plasma levels who do not receive antidote therapy range from 3% to 4%. In nonfatal cases, serial liver biopsies and liver function tests have shown prompt resolution with no significant residual functional or architectural alterations of the liver.

4.5 Situations of Potential Acetaminophen Overdose and Misadministration

Untreated acetaminophen overdoses (single doses of ≥15 grams) can produce hepatotoxicity. Acetaminophen hepatotoxicity occurs as a threshold effect and is characterized by a lack of toxicity at lower/therapeutic doses. Acetaminophen hepatotoxicity occurs after major depletion of glutathione, an endogenous detoxifying substance. Once the threshold is exceeded, increasing acetaminophen doses may produce increasing degrees of hepatotoxicity, unless NAC (antidote) is administered. This threshold is not likely to be reached at single doses of less than 15 grams of acetaminophen [Mitchell 1974].

Situations in which acetaminophen overdose and resultant hepatotoxicity may occur include acute intentional overdose and repeated supratherapeutic overdose in adults and acute accidental ingestion or overdose and repeated supratherapeutic overdose in children. These situations are summarized in the following sections.

4.5.1 Acute Intentional Overdose in Adults – Suicide Gestures or Attempts

Adult and adolescent intentional overdoses, either as a suicide gesture or attempt (whether successful or unsuccessful), cause most of the serious cases of acetaminophen hepatotoxicity. This conclusion is based on data sources summarized in detail in Section 4.6, Data Sources Available to Assess Misadministration and Overdose. The frequency of suicide as a reason for overdose may be higher than reported since suicidal intent is difficult to confirm. Disclosure of suicidal intent may be of concern given possible repercussions (eg, loss of insurance coverage, privacy, social stigma and family impact). An effective antidote treatment (NAC) and strategy for treating cases of acetaminophen overdose have greatly reduced morbidity and mortality from intentional and unintentional overdose.

4.5.2 Repeated Supratherapeutic Overdose in Adults

Another form of overdose is that of repeated supratherapeutic ingestion. In these cases, consumers report repeat doses of multiple products containing acetaminophen or repeat

dosing of more than the recommended single dose of acetaminophen. These practices may result in a substantial and serious acetaminophen overdose.

Two case series of repeated supratherapeutic overdoses have been recently reported, one from the United States [Dart 2000] and the second from the United Kingdom [Dargan 2002]. These cases were evaluated to identify if and when therapeutic interventions for acetaminophen overdose might be required. The United States case series [Dart 2000] identified two groups of patients based upon clinical presentation: 1) those with elevated liver function tests on presentation; and 2) those with normal liver function. Patients presenting with normal liver function tests were not treated with a course of NAC, and there was no subsequent evidence of hepatotoxicity. Among the patients presenting with abnormal liver function tests, all were started on NAC therapy and 32.5% of these patients with abnormal liver function tests developed liver failure; one patient required a liver transplant and four patients died. The authors concluded that patients who present after repeated supratherapeutic overdoses with normal liver function may not need treatment with NAC.

In the United Kingdom case series [Dargan 2002], the mean reported acetaminophen dose ingested was 17.7 grams and the mean time from the first acetaminophen dose to presentation was 32 hours. Seventeen of the 19 cases received NAC; two cases did not. Notably, in this case series none of the 19 patients developed serious sequelae.

4.5.3 Acute Accidental Overdose in Pediatric Patients

Acute accidental ingestion or overdose may occur in young children because of the widespread availability of acetaminophen in American households. Reports from the AAPCC indicate that even though there are large numbers of exposures to pediatric dosage forms, very little toxicity follows from such exposures. Even accidental ingestion of adult dosage forms of acetaminophen in children infrequently produces toxicity, in part because the dose actually absorbed is usually below the threshold for toxicity.

In a recent five-year period (1996-2000), AAPCC reported 217,170 exposures to acetaminophen-containing products in children less than six years of age. There were three fatalities in children less than six years of age and one fatality in an 11-year-old child [Litovitz 1997; Litovitz 1998; Litovitz 1999; Litovitz 2000; Litovitz 2001]. McNeil obtained additional details from the AAPCC for 1997 and learned that of 49,873 exposures to acetaminophen-containing products in children less than six years of age, there were 256

exposures in which NAC treatments were reportedly administered [personal communication from AAPCC, September 27, 2001]. These more serious exposures represent about 0.5% of the reported exposures in children that year. Toxicity is rare following acute accidental overdose in children.

4.5.4 Repeated Supratherapeutic Overdose in Pediatric Patients

Repeated supratherapeutic overdose in pediatric patients has been described when parents or caregivers repeatedly gave more than the recommended acetaminophen dose, resulting in a substantial acetaminophen overdose. 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. We are concerned about these potential cases of inadvertent overdose. As such, in 1999 McNeil submitted a Citizen's Petition to the FDA requesting an expansion of the OTC labeling of pediatric acetaminophen products to include dosing instructions for children under 2 years of age.

4.6 Data Sources Available to Assess Misadministration and Overdose

This section summarizes the FDA AERS Data Set and other data.

- Case reports are the source of serious hepatic events associated with acetaminophen exposure. These reports are observational and therefore cannot be used to establish causality.

- The number of serious reports for acetaminophen products at the FDA is disproportionately large relative to other monograph analgesics because: a) FDA regulations do not require AERS reporting for OTC monograph drug products, and b) McNeil has submitted serious reports for all single-ingredient acetaminophen products and reports of death for acetaminophen combination products, including published literature and fatalities from AAPCC.

The data sources available to assess the misadministration and overdose situations described in Section 4.5, Situations of Potential Acetaminophen Overdose and Misadministration, include spontaneous reports submitted to the FDA's Adverse Event Reporting System (AERS), poison control center reports, the Drug Abuse Warning Network (DAWN), and reports from liver transplant centers. These data sources are descriptive in nature and consist of case reports. This section places the case reports in the hierarchy of

medical evidence, reviews the data from the available sources, and summarizes inferences from these data.

4.6.1 Quality of Data

The ability to accurately assess risk depends on the quality of the data available for evaluation. The quality of medical evidence can be categorized as being from analytical studies (randomized controlled trials, cohort studies, case-control studies) or from descriptive studies (correlational studies, cross-sectional surveys, case series, and case reports) [Hennekens 1987]. Information from analytical studies is more likely to be useful in establishing causal associations than information from descriptive studies, from which causation cannot be assessed. Spontaneous reports sent to manufacturers and regulatory authorities are useful for signaling the possibility of rare unexpected adverse drug reactions that are not detected during pre-marketing testing, and for providing potential patient risk factors (such as drug interaction, age) associated with drug reactions [Faich 1986; Stang 1992]. Properly designed epidemiological studies may be useful to evaluate potential signals suggested by spontaneous reports and for quantifying relative risk associated with specific drug exposures. While randomized controlled trials are unlikely to include a sufficient number of subjects for detection of rare adverse drug events, they are useful for exploring specific causal relationships.

Spontaneous adverse event reports have limitations that are well recognized (see below). AERS, the FDA's database for spontaneous adverse drug experience, is referenced, where appropriate. Lack of reliable dose information and the intentionality in overdose, as identified below, are applicable not only to spontaneous reports, but also to data from most case reports and liver transplant centers.

Causality Assessment. Causality assessment is impeded by the limited quality [Goldman 1998] and incompleteness of data in spontaneous reports, despite diligent efforts by manufacturers to obtain follow-up information from reporters. Spontaneous reports rely on retrospective data collection and as such are often missing important clinical information and laboratory results.

Dose Information and Intentionality in Overdose. Dosing information provided in spontaneous reports relies on the reporter's ability to recall information conveyed to the reporter by healthcare professionals during the reporting process, and the reporter's motivation to correctly report. The lack of precise dose information and uncertain reliability

regarding intent of drug use (overdose, misuse, therapeutic intent, etc) make it impossible to assess the relationship between dose and drug reaction. This is of particular concern with acetaminophen because dosage information is key to assessing the likelihood of drug toxicity, and whether a plausible threshold for overdose was exceeded. OTC analgesics are often taken on an as-needed basis by consumers who do not typically keep a record and accurately report how much or how often they take their medications. Even when the reports originate from healthcare professionals, the dosing information comes ultimately from consumers or the family members of affected individuals. In addition, even if plasma levels are available, the absence of a reliable time interval between acute ingestion of acetaminophen and blood drawing limits the utility of acetaminophen levels. When reported, very high plasma concentrations may refute the reported dose and suggest that a large overdose was taken. Given the social stigma associated with suicide attempts and concerns regarding insurance coverage in the United States, intentional overdose may be reported as accidental.

Reporting Bias. Safety signal detection as proposed by International Committee on Harmonization is based on review of individual reports, or on the reporting frequency of a given adverse event relative to a reference (either all drugs in the entire database or a select few for the same indications). The frequency of reporting of a given adverse event can be skewed by numerous factors including publicity through educational efforts, media and literature, as well as the reporting practices of various manufacturers [Stang 1992]. Spontaneous reports are an unreliable measure of risk, since they may reflect the relative awareness of specific toxic effects among reporters [Miwa 1997]. As an example, an apparent differential risk of gastrointestinal and dermatological events for NSAIDs suggested by a review of spontaneous reports was not corroborated by epidemiologic studies.

Manufacturers of monograph OTC analgesics are not required by FDA regulation to submit adverse event reports to AERS. Any manufacturer electing to submit such reports could create a false signal by doing so. OTC ibuprofen and naproxen sodium analgesic products are marketed under the NDA process and therefore have more stringent adverse event reporting requirements than aspirin or acetaminophen, which are marketed under the Tentative Final Monograph for Internal Analgesic, Antipyretic and Antirheumatic products. While not required under the monograph process to submit adverse event reports for regular or extra-strength acetaminophen (monograph products), as an NDA holder of extended release acetaminophen, McNeil submits to the FDA serious reports for all single-ingredient acetaminophen products; McNeil also voluntarily submits to the FDA reports of

death for all monograph Tylenol® combination products. McNeil scans the world literature for reports of acetaminophen events, regardless of brand name, dosage form, country of origin, or case verification. McNeil also reports AAPCC annual fatality table cases as individual case reports. Furthermore, McNeil submits any consumer reported event, whether or not the event is verified. Thus, the number of serious reports for acetaminophen products at the FDA is disproportionately large relative to other monograph analgesics.

Underreporting. Reports in spontaneous reporting systems are either submitted to the manufacturer and subsequently, to regulators, or voluntarily reported directly to regulators. It is generally believed by regulatory authorities that there is an underreporting of adverse events [Goldman 1998]. This may be more pronounced for OTC products marketed under the monograph process, for which there are no regulatory reporting requirements. Thus, the incidence of drug-related adverse events cannot be determined from spontaneous reporting systems [Goldman 1998], and the number of reports in such a database do not reflect the incidence of the event in the population exposed.

In summary, case reports are limited by their anecdotal and retrospective nature, quality and incompleteness of data, reliance on patient's ability to recall information on dosing and the true intention of overdose, and the effects of reporting bias and underreporting. For acetaminophen, this is further complicated by the fact that acetaminophen toxicity occurs only after a threshold dose has been exceeded, so that an accurate, reliable dosage history is critical for any evaluation.

4.6.2 Spontaneous Reports Selected by the FDA for Evaluating the Hepatotoxicity of Acetaminophen (FDA AERS Data Set)

4.6.2.1 Background

FDA has identified a set of AERS reports with serious outcome reported during the time period January 1998 through March 2001 that include selected "hepatic" adverse event terms and acetaminophen as a suspect drug. Stated exclusions were reports from foreign sources and duplicate reports; reports with hepatic cancer terms, reports with suicide or intentional overdose terms; reports with concomitant drugs that were removed from the market for hepatotoxicity; and those reports with more than two non-acetaminophen suspect drugs. This specific FDA-selected AERS Data Set was developed in an attempt to determine the circumstances that led to hepatotoxicity. A total of 307 reports, identified by FDA from AERS over this time period, were provided to the Consumer Healthcare Products

Association (CHPA) under a Freedom of Information request. McNeil subsequently obtained the MedWatch forms from CHPA.

4.6.2.2 Analysis of FDA-Selected Reports

McNeil has reviewed and analyzed the FDA-selected AERS Data Set. McNeil noted discrepancies regarding stated exclusion criteria. One report did not involve acetaminophen as a suspect drug. There was one report of intentional self-injury and four reports were apparently from foreign sources, indicated by the term paracetamol as the suspect medication, describing intravenous NAC protocols or intravenous acetaminophen, a formulation not available in the United States. The manufacturer's received date ranged from November 28, 1994 to August 2, 2001. Additionally, reports were included from the AAPCC TESS database dating back to 1987. At least one third of the events occurred during the time period from 1979 through 1997. To put in perspective these events that took place over 25 years, it should be noted that in 2001 purchases of OTC single-ingredient adult acetaminophen tablets were approximately 11 billion, of OTC combination-ingredient adult acetaminophen tablets were approximately nine billion, and approximately three billion prescription were filled for acetaminophen-containing products; purchases/perscriptions in earlier years were less.

The FDA-selected AERS Data Set (306 reports) is referred to herein as the "FDA AERS Data Set". The 281 adult reports are discussed in Section 4.6.2.2.1, FDA AERS Data Set – Adult Reports, and the 25 pediatric reports are discussed in Section 4.6.2.2.2, FDA AERS Data Set – Pediatric Reports.

4.6.2.2.1 FDA AERS Data Set – Adult Reports

This AERS Data Set was selected by FDA to understand reports that may reflect inadvertent adverse outcomes or misuse. FDA intended to exclude obvious suicide, usually associated with very large drug ingestions. Thus, the reported dosage (which could only be estimated in 48% of the reports in the data set) is skewed significantly toward labeled directions for use, consistent with reports of inadvertent use or misuse.

This selective data set cannot be used to determine an acetaminophen toxicity threshold for any condition (ie, concomitant drug, alcohol history, or pre-existing concomitant disease) or to establish intent.

Table 4-3 provides a summary of the distribution of the 281 adult reports in the FDA-selected Data Set by product category, ie, the type of acetaminophen-containing product, (single-ingredient, multiple ingredient, OTC, and prescription) used. Use of acetaminophen-containing prescription combination analgesics accounted for 37% of the reports.

Table 4-3. Distribution of Reports by Product Category

Drug Product Category	Number of Reports	% of Total Reports
OTC Acetaminophen Single Ingredient alone	153	54.4%
*OTC Acetaminophen Combos + OTC Acetaminophen Single	14	5.0%
OTC Acetaminophen Combos	9	3.2%
Rx Acetaminophen Combos	57	20.3%
*Rx Acetaminophen Combos + OTC Acetaminophen Single	48	17.1%

Overall, 24.5% of the reports involved the concurrent ingestion of two or more acetaminophen-containing products. The majority of these reports were found in the two categories identified in Table 4-3 with an asterisk. In addition, other reports of concurrent ingestion were included in this percentage, eg, use of multiple OTC single-ingredient acetaminophen products, use of multiple Rx acetaminophen combination products.

The quality of these reports with respect to the presence or absence of important data elements that could be used to infer drug relationship to reported hepatotoxicity was evaluated. One hundred sixty-eight (168) reports did not have sufficient information to allow for an estimate of the dose taken. Eighty-eight percent (88%) of these reports did not contain liver pathology information. Seventy-eight percent (78%) of these reports did not report viral hepatitis testing; of the 61 that did, 48% (29) were positive for hepatitis A, B, or C. In addition, 38% (108) of the reports did not contain AST or ALT levels. Reported alcohol use or abuse among the cases was frequent. Among the 281 reports, 116 contained information on alcohol use or blood alcohol level, 76 of which had a history of chronic alcohol ingestion up through the time of ingesting acetaminophen.

FDA Subsets. FDA theorized that three factors, ethanol use, underlying/history of liver disease, and potentially hepatotoxic co-suspect medications, increase susceptibility to acetaminophen-associated hepatotoxicity at lower than expected doses. For these report subsets, FDA calculated the mean and median acetaminophen reported dose separately for cases with and without the factor. These factors, however, appear to be groupings in which lower doses of acetaminophen use may be coincidentally associated with reports of

hepatotoxicity from other causes, or, in some cases, reports in which the reported dose grossly underestimates actual acetaminophen exposure in some cases. A more-detailed description is provided below.

- *Ethanol Use.* It is well known that the alcoholic person underreports alcohol use [Broughan 2000] and may experience short-term memory deficits. Recall of other drug use may also be inaccurate. The excessive use of ethanol may also extend into excessive use of other substances, including acetaminophen. (See Section 4.3.1, Situations in Which Cytochrome P-450 2E1 Might Be Induced, for a discussion of alcohol-related issues.) Nevertheless, the caution to have anyone who consumes three or more alcoholic drinks every day talk with their doctor before using acetaminophen or other pain relievers remains appropriate and the need to strongly urge chronic alcoholics not to exceed the recommended dose is very important.

- *Underlying or History of Liver Disease.* Underlying liver disease also confounds attribution, since pathophysiology of the underlying disease progression and accompanying discomfort may lead an individual to self-medicate with OTC analgesics, including acetaminophen. In fact, one would expect confounding by indication. Frequency of therapeutic acetaminophen use would be expected to be higher in persons with liver disease because other analgesics are frequently contraindicated. In particular, individuals who take acetaminophen for their pain and have underlying liver disease are likely to be using recommended doses and would be expected to accurately report a lower average dose. This association is not causal. The pathophysiology of their underlying liver disease progression or liver failure, however, may be unrelated to the use of acetaminophen.

- *Potentially Hepatotoxic Co-Suspect Medications.* Many of these cases were submitted to FDA primarily for the co-suspect drug and patients were taking acetaminophen to treat symptoms associated with their underlying illness. This association is not causal.

While we believe that it is impossible to determine accurate dose from case reports and disagree with relying upon an analysis of acetaminophen dose from case reports, we explored FDA's analysis of acetaminophen dose for the subsets of cases with alcohol use and liver disease history.

We calculated the mean and median acetaminophen dose (mg/day) by alcohol use group (yes, no, or unknown) and found no statistically significant difference among the groups (ANOVA p= 0.85). Further, when the "unknown" alcohol use group was alternately combined with the "yes" and "no" alcohol use categories, again, there were no statistically significant differences between the groups (unknown combined with yes, p= 0.57; unknown combined with no, p= 0.82).

We performed the same analysis for underlying liver disease. We calculated the mean and median acetaminophen dose (mg/day) by underlying liver disease group (yes, no, or unknown) and found no statistically significant difference among the groups (ANOVA p= 0.54). Further, when the "unknown" underlying liver disease group was alternately combined with the "yes" and "no" underlying liver disease categories, again, there were no statistically significant differences between the groups (unknown combined with yes, p= 0.78; unknown combined with no, p= 0.32).

In summary, we believe that it is impossible to determine accurate dose from case reports and disagree with relying upon an analysis of acetaminophen dose from case reports. Further, our statistical analysis demonstrates that the trends FDA reported with these data are not systematic and no relationship between these factors and the reported acetaminophen dose is evident. For all of these reasons, these analyses do not support the theory that these factors increase susceptibility to acetaminophen-associated hepatotoxicity.

Expert Review Panel Causality Attribution of Adult Reports. Case reports are descriptive and cannot be used to establish causality. To prevent evaluation bias and to assist identification of important signals contained in this dataset, McNeil undertook to assess the nature of identifiable factors among these reports. To do this, McNeil convened a group of nine outside medical experts, representing toxicology, hepatology, and emergency medicine to review the 281 adult reports. Attachment 1 contains the complete listing of the names and affiliations for each member of the Expert Review Panel. The panel of medical experts was asked to determine if each report was evaluable, and if so, the likelihood that the reported hepatic event was related to acetaminophen. Reports were considered evaluable if there was mention of acetaminophen use anywhere in the report and the case findings indicated or demonstrated any degree of liver injury or disease. All but three of the cases were considered to be evaluable.

After considering criteria used by others to evaluate adverse drug reactions, the panel developed their own causality data collection instrument [see Attachment 2] since existing methodologies (The Roussel Uclaf Causality Assessment Method and the Clinical Diagnostic Scale) require more data than are available on the FDA 3500A MedWatch reports, and were not directly applicable to acetaminophen overdose toxicology.

Each medical expert reviewed all 281 reports independently, assigned a probability category, and submitted a report assessment sheet for each case, noting the basis for their judgement. This was done by all participants prior to a final consensus meeting. At the consensus meeting, the panel reviewed each report as a group, and reached a consensus regarding the probability category for each report. Additionally, the panel was asked to provide overall observations on the process and data set. Table 4-4 provides a summary of the number of reports classified into each of the categories. As shown in Table 4-4, 73 (26%) reports did not contain sufficient information for determination. Of the 205 reports with sufficient information, 38% were considered to have more than a 50% likelihood (probably or definitely categories) of being related to acetaminophen exposure.

Table 4-4. Summary of Expert Review Panel Consensus Probabilities of Acetaminophen Exposure Being Related to Hepatic Events in the FDA Data Set

Probability category	Number of Reports
Definitely	3
Probably	74
Possibly	47
Unlikely	53
Definitely not	27
Data are insufficient	73
Not evaluable	3
No consensus	1
Total number of reports	281

McNeil further evaluated all reports with an Expert Review Panel designation of ≥50% probability of acetaminophen related liver abnormality (Definitely and Probably). We evaluated these reports for identification of descriptive factors that could, taken together with consumer medication usage information, lead to effective interventions and reduction in adverse outcomes (as described later in Section 6, McNeil Initiatives and Recommendations). These reports were also classified against FDA's severity criteria (FDA Briefing Document. Nonprescription Drugs Advisory Committee Meeting, September

19 – 20, 2002; http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882b1.htm, access confirmed August 30, 2002), Categories 1 to 4, and found to be positively correlated (0.24, $p<0.001$).

As shown in Table 4-5, the cases assessed by the Expert Review Panel to be definite or probable (n= 77) included individuals who were younger and had reported a history of alcohol use or alcohol abuse (alcoholism) when compared with the remaining reports (n=204).

Table 4-5. Demographic Characteristics of FDA-Selected AERS Data Set Grouped by Expert Review Panel-Probability Categories

	Definite/Probable Cases[a] (N = 77)	All Other Cases (N = 204)	p-Value[b]
Mean age, years	40.1	45.2	0.0192*
Gender, no. (%)			
Female	53 (68.8)	119 (58.3)	
Male	24 (31.2)	78 (38.2)	0.1947
Unknown	0 (0)	7 (3.4)	
Product type, no. (%)			
OTC APAP single ingredient	41 (53.2)	112 (54.9)	
OTC APAP combination	4 (5.2)	5 (2.4)	
OTC APAP combination + OTC APAP	4 (5.2)	10 (4.9)	0.7983
Rx APAP combination	14 (18.2)	43 (21.1)	
Rx APAP combination + OTC APAP	14 (18.2)	34 (16.7)	
History of alcoholism or alcohol, no.(%)			
Yes	40 (51.9)	56 (27.4)	
No	7 (9.1)	32 (15.7)	0.0087*
Unknown	30 (39.0)	116 (56.9)	
Pre-existing liver disease, no. (%)			
Yes	15 (19.5)	32 (15.7)	
No	6 (7.8)	22 (10.8)	0.3279
Unknown	56 (72.7)	150 (73.5)	
Pre-existing kidney disease, no. (%)			
Yes	1 (1.3)	8 (3.9)	
No	6 (7.8)	20 (9.8)	0.4392
Unknown	70 (90.9)	176 (86.3)	
Human immune deficiency status, no. (%)			
Yes	0 (0)	4 (2.0)	
No	6 (7.8)	22 (10.8)	0.3044
Unknown	71 (92.2)	178 (87.3)	

a: Cases ranked by Expert Review Panel as being ≥50% attributable.
b: ANOVA for age, chi-square test for all other comparisons (unknowns not included).

The type of products used in both groups was similar; approximately half of the reports included use of an OTC single-ingredient acetaminophen product. Both groups were comprised of more women than men (58.3% to 68.8%). As expected with these types of incomplete reports, all categories contain some “unknowns.”

There was no significant difference between the definite or probable reports and all other reports for pre-existing liver or kidney disease or HIV. In addition, there are well-controlled prospective data indicating that in individuals with liver or kidney disease, acetaminophen can be used safely with no dose adjustment (see Section 4.2, Use of Recommended Doses in Selected Populations).

However, history of alcoholism appears to have been reported more frequently in the definite or probable groupings. The only prospective data available [Kuffner 1997, 2001] demonstrate that chronic alcoholics can take recommended doses of acetaminophen (up to four grams per day) without added risk of liver injury. The caution to have anyone who consumes three or more alcoholic drinks every day talk with their doctor before using acetaminophen or other pain relievers remains appropriate, and the need to strongly urge chronic alcoholics not to exceed the recommended dose is very important.

Table 4-6 provides a summary of the demographic characteristics for those cases assessed by the Expert Review Panel to be definite or probable and included a single-ingredient OTC acetaminophen product (n= 41) and definite or probable cases that included a prescription acetaminophen combination product (n= 28) as a suspect drug. Both groups of reports had more women than men (67.9% to 70.7%). As expected with case reports, all categories contain some “unknowns.” Mean age was significantly lower in the OTC single-ingredient group when compared to the prescription product group.

Of the OTC single-ingredient acetaminophen products, 52% had no dose or dosage form specified, 37% were 500 mg dosage forms, 10% were 325 mg and a single report listed 650 mg extended release. This is consistent with the most widely distributed dosage form, 500 mg. In these cases, other suspect drugs listed were alcohol (7) and cocaine/opiates/phenobarbital/ benzodiazepine (6).

Of the prescription acetaminophen combination products, 50% were used with single-ingredient acetaminophen products and 50% were used alone. In the prescription combination product only category, two reports described non-therapeutic use of large doses of the prescription ingredient, leading to acetaminophen overdose. When additional acetaminophen was taken along with the prescription acetaminophen combination, the additional acetaminophen product was infrequently specified as to dosage strength. Prescription combination product ingredients included hydrocodone (9) codeine (9) oxycodone (5) propoxyphene (5).

Table 4-6. Demographic Characteristics for OTC Single Ingredient and Prescription Acetaminophen Product Subcategories of Expert Review Panel-Ranked Definite/ Probable Cases[a] from FDA-Selected AERS Data Set

	OTC Single Ingredient Product (N = 41)	Prescription Product[b] (N = 28)	p-Value[c]
Mean age, years	38.1	44.9	0.0448
Gender, no. (%)			
Female	29 (70.7)	19 (67.9)	0.7970
Male	12 (29.3)	9 (32.1)	
History of alcoholism or alcohol, no.(%)			
Yes	21 (51.2)	13 (46.4)	
No	4 (9.8)	3 (10.7)	1.000
Unknown	16 (39.0)	12 (42.9)	
Pre-existing liver disease, no. (%)			
Yes	7 (17.1)	6 (21.4)	
No	2 (4.9)	4 (14.3)	0.6285
Unknown	32 (78.0)	18 (64.3)	

a: Cases ranked by Expert Review Panel as being ≥50% attributable.
b: Includes use of a prescription acetaminophen combination product alone or together with an acetaminophen OTC product.
c: ANOVA for age, Fischer's Exact test for all other comparisons (unknowns not included).

Only three of the 205 reports (1.5%) were considered by the medical experts to be definitely related to acetaminophen. All had a history of self-abusive behavior - an apparent bulimic and two alcoholics. All appeared to involve substantial overdoses, but intentionality could not be determined. A brief description of these three cases follows.

One of the reports involved ingestion of 14.5 grams in one day by a 16-year-old female to induce nausea/vomiting. She had a five-to-seven day history of inducing nausea/vomiting. She was treated with NAC and was discharged.

The second report involved a consumer with a history of drinking six to eight beers in an average day. Over the week prior to admission, he took approximately 110 Sinutab® and acetaminophen 500-mg tablets combined. Sinutab® tablets contain 500 mg of acetaminophen. He was treated with NAC and received a liver transplant. He developed septicemia following the transplant and died.

The third report was a 62-year-old female with a history of chronic alcohol use (estimated 60 grams per day for 40 years) and hepatitis C, who reportedly ingested 1 to 1.5 grams per day of acetaminophen for shoulder pain during the four days preceding admission. However, at an unspecified time post-ingestion, the plasma acetaminophen level was reportedly 158.9 ug/mL. Assuming her weight was 60 kg and the volume of distribution was 1 L/kg, this would equate to a body burden of 9.5 grams, consistent with a substantial overdose. She was treated with NAC, gradually improved and was discharged.

Dose cannot be verified in this data set. Fifteen (15) reports were considered by the experts to have a ≥50% likelihood of attribution to acetaminophen with a reported dose of less than 8 grams per day. When available, however, plasma levels did not confirm the reported doses, often suggesting a body burden vastly in excess of the reported dose.

4.6.2.2.2 Conclusions from the FDA Selected AERS Data Set of Adult Reports

Despite significant limitations to the reports in the FDA selected AERS Data Set, the available information supports the following conclusions:

- The AERS spontaneous reporting system serves as a signal generating system for rare, unexpected adverse events in marketed products. It cannot be used to determine event rates, dose, or intentionality.
- The three AERS reports that McNeil's Expert Review Panel found to be definitively associated with acetaminophen involved substantial overdose in individuals with self-abusive behaviors (alcohol abuse, bulimia).
- McNeil's Expert Review Panel concluded that most of the cases with a ≥50% likelihood of attribution to acetaminophen use were associated with substantial overdoses.
- Hepatic effects, although reported at recommended therapeutic doses in the FDA-selected Data Set, were impossible to confirm given the limitations of the available information.
- Formulations most commonly reported were OTC single-ingredient and Rx combination acetaminophen products. OTC acetaminophen combination products were rarely reported.
- Alcohol and alcohol abuse were reported more often in reports assigned a ≥50% probability of acetaminophen attribution.

4.6.2.2.3 FDA AERS Data Set – Pediatric Reports

Twenty-five of the total of 307 reports identified by FDA from AERS were pediatric reports. Of these 25 pediatric reports, four involved an unintentional single ingestion in which an unsupervised child ingested an acetaminophen product and three reports were of maternal overdoses. Because these seven reports were not reports of misadministration to children, they are not described further.

The remaining 18 reports were divided into two categories:

- Those reports involving the ingestion of one *single-ingredient acetaminophen product (n = 16)*.
- Those reports involving the ingestion of two *acetaminophen-containing products (n = 2).*

Each category of reports is described below.

Reports Involving the Ingestion of One Single-Ingredient Acetaminophen Product. Sixteen of the 18 reports involved the ingestion of one single-ingredient acetaminophen product. Twelve of the 16 reports involved children less than two years of age.

- In seven reports, infant drops were administered using a device other than the supplied dropper and resulted in unintended overdose. Five of the 12 resulted in death; six recovered, and in one the outcome is unknown. In four of the five cases that resulted in death, the acetaminophen dose reported was in excess of the recommended dose. The remaining fatality reported use of acetaminophen at a dose "normal dose for his weight," however, the reporter indicated that the child's primary physician did not attribute the death to acetaminophen. When the reported doses were converted to daily exposure by weight, the doses ranged from 233 to 375 mg/kg/day given for periods from less than one day to four days. However, in some instances, the dose was not clearly defined or the duration not specified.

The four remaining reports were in children between two and eight years of age.

- One report was of an eight-year-old whose mother admitted to giving the child "at least 10 double strength Tylenol® tablets within less than 24 hours". This would exceed the recommended dose for an adult. Extra Strength Tylenol® is not labeled for use in children under 12 years of age.

- Three of these four reports involved the use of single-ingredient acetaminophen at recommended dose, but other potentially hepatotoxic medications (Dilantin® and Zithromax®) were also being given. There was no clinical evidence that the reported events were causally related to the acetaminophen use.

Reports Involving the Ingestion of Two Acetaminophen-Containing Products. Two of these 18 reports involved the ingestion of two acetaminophen-containing products. Neither of the two cases had dosing information available.

- One involved a three-year-old child who was given both OTC and prescription formulations containing acetaminophen for four to five days. A drug screen was positive for pseudoephedrine, dextromethorphan, and codeine. The child died three days after presentation to the hospital.
- One involved an 11-month-old infant given acetaminophen as a suspension, in suppositories, and as part of a multi-symptom cold remedy. The infant received a 72-hour course of NAC therapy and progressed to a full recovery.

Previous Summary of FDA SRS and AERS - Pediatric Misadministration Reports. At FDA's request, McNeil provided to the FDA in December 2000 a report on all pediatric cases of misadministration (domestic and international) that were previously reported to the FDA for the period January 1, 1992 through August 31, 2000. During the more than eight-year period, there were 117 reports of misadministration in children. Eighty-six (86) of the 117 reports involved misadministration of pediatric dosage forms, usually in children less than two years of age for which dosing information is not on the label. Fifty (50) of the 86 reports involved misuse of the more concentrated infants' drops in place of the less concentrated children's liquid [McNeil Submission to FDA 12/20/00]. McNeil's introduction in 1999 of the SAFE-TY-LOCK integrated infant dropper/bottle helps prevent dispensing of infant drops in teaspoons or similar imprecise dosing devices. The effect of this dropper/bottle innovation on the number of such reports is described in Section 6.2.2, Previous Initiatives: Programs to Reduce Misadministration of Pediatric Acetaminophen Products.

4.6.2.2.4 Conclusions From the FDA AERS Data Set of Pediatric Reports

An analysis of the FDA AERS Data Set of pediatric reports clearly indicates that the majority of cases involved situations where the child was given substantial overdoses of a single-ingredient pediatric acetaminophen product. The most frequently involved dosage form was the acetaminophen drops formulation for which McNeil has implemented a risk management plan (see Section 6.2.2, Previous Initiatives: Programs to Reduce

Misadministration of Pediatric Acetaminophen Products). Eleven of the 12 reports involving the acetaminophen single-ingredient products were in children less than two years of age. In 1999, McNeil submitted a Citizen's Petition to FDA requesting labeled dosing for children less than two years of age on pediatric liquid formulations.

4.6.3 Poison Control Center Data Sets

The AAPCC Toxic Exposure Surveillance System (TESS) database includes reports of human exposures to various substances (eg, pharmaceutical products, cleaning substances, chemicals, foods, and plants) submitted by poison control centers [Litovitz 2001] across the United States. Reports are received from consumers and health care professionals via telephone. Callers typically request advice and treatment recommendations.

Call information is not verified or clarified by medical record review or other means. With respect to fatality case reports, poison control centers provide no causality probability or assessment that the reported substance(s) contributed directly or indirectly to the fatal outcome. Nevertheless, TESS is the largest single data set of reported acetaminophen exposures, and a review of recent data provides a broad perspective. In addition to the general data published by AAPCC, we also obtained a year's worth of case-specific information about pediatric misadministration reports from two poison control centers in an effort to understand causal factors that might contribute and be amenable to intervention.

Our review found the following:

- Among acetaminophen alone exposure with known outcome, 96% did not result in major effects, and less than 0.5% of these reported exposures (including suicidal overdose) were known to result in death.
- Half of the exposure reports pertain to single-ingredient acetaminophen products and the other half to combination acetaminophen products.
- Although about half of the single-ingredient acetaminophen exposure reports pertain to children six years of age or younger, there was less than 1 known death per year for the period of 1996 to 2000.
- Pediatric misadministration rarely results in serious outcome. Rare events could be further prevented by permitting dosage information for children under two on the product label.

4.6.3.1 AAPCC TESS Data Set

In the AAPCC TESS database, an exposure is defined as a call to the poison control center regarding administration of, or contact with, a substance, but does not necessarily involve toxicity. Reasons for exposure are coded using categories that include intentional exposure (suspected suicidal, intentional abuse, intentional misuse or intentional unknown), unintentional exposure (unintentional general, therapeutic error, unintentional misuse, or unintentional unknown), and adverse reaction. Medical outcomes are also coded by category: unknown, no effect, minor effect, moderate effect, major effect, and death [Litovitz 2001]. Major effect involves signs or symptoms that are life-threatening or an outcome of significant disability or disfigurement.

As shown in Table 4- 7, in the year 2000 [Litovitz 2001], 108,066 acetaminophen exposures in adults and children were reported to 63 poison control centers serving a population of 270.6 million in the United States. For single-ingredient acetaminophen products alone, there were 856 exposures in adults and children with a major effect (3.4% of 25,101 exposures with known outcomes). Ninety-nine (99) deaths were reported to be associated with single-ingredient acetaminophen products. One hundred and eleven (111) deaths were reported associated with acetaminophen combination products (85 episodes were associated with opioid-containing acetaminophen products, representing 40% of all acetaminophen-associated deaths).

Table 4- 7. Acetaminophen Exposure Data Based On AAPCC 2000 Annual Report

		Age in Years (%)[a]			Reason for exposure (%)[b]		Outcome (%)[c]	
Product	Total Exposures	<6	6-19	>19	Unin-tentional	Inten-tional	Major	Death
Acetaminophen only	56, 371	47.1	26.7	26.2	65	35	3.41	0.39
Adult formulation	28,009	22.8	37.2	40.0	46.5	52.5	3.62	0.37
Pediatric formulation	20,629	89.0	9.6	1.4	97.6	1.9	0.41	0.02
Unknown formulation	7,733	22.5	34.3	43.2	41.1	57.7	6.15	0.90
Acetaminophen in combination with other drugs	51,695	15.7	20.9	63.4	38.1	57.1	4.2	0.4

a: Age – expressed as % of all exposure cases in which the age was known for each acetaminophen formulation
b: Reason for exposure – expressed as % of all exposure cases in which the reason was known for each dose formulation
c: Outcome – expressed as % of all exposure cases with known outcome for each dose formulation

Pediatric Data - AAPCC. As shown in Table 4- 7, also in 2000, children six years of age or younger accounted for 47.1% and 15.7% of the reported exposures to single-ingredient acetaminophen and acetaminophen combination products, respectively. In a recent five-year period (1996-2000), the AAPCC reported 217,170 exposures to acetaminophen-containing products in children less than six years of age. There were three fatalities in children less than six years of age and one fatality in an 11-year-old child [Litovitz 1997; Litovitz 1998; Litovitz 1999; Litovitz 2000; Litovitz 2001]. McNeil has obtained additional detail from the AAPCC for 1997 and found that of 49,873 exposures to acetaminophen-containing products in children there were 256 exposures in which NAC was reportedly administered to children under six years of age [personal communication from AAPCC, September 27, 2001]. This represents 0.5% of childhood acetaminophen exposures that led to hospitalization and treatment with NAC. These data suggest that while pediatric exposures are common, the actual proportion of cases where there is a need for other than routine induction of emesis or similar measures is rare.

In a separate analysis of TESS data for acetaminophen-associated episodes in children less than six years of age (data not shown above), it is noted that of the 117,892 episodes received during the period 1998 to 2000, over 99% were unintentional overdose. Sixty-five (65) episodes (0.055%) were associated with major adverse effects.

Intentionality of Overdose Exposure – Five-Year AAPCC Data. AAPCC annual report data for single-ingredient acetaminophen during a recent five-year period (1996-2000) were reviewed. Table 4-8 provides a summary of the 213 fatal outcomes reported to AAPCC involving single-ingredient acetaminophen during a recent five-year period (1996-2000), the percentage reporting unintentional exposure reasons was small.

Approximately 16% of 190 reports that specified a reason reported unintentional reasons (therapeutic error or unintentional unknown). During this period, the frequency of intentional overdose (intentional misuse, intentional abuse, intentional unknown) was 32% and of intentional suicide was 52%. Thus, intentional overdose accounted for 84% of overdose with known intentionality. This is consistent with data from the National Hospital Discharge Survey for the period 1990 to 1999. In this survey, acetaminophen overdose was intentional in 74% of the patients, and intention was unknown in 18% of the patients.

Table 4-8. Exposure Reasons for the 213 Single Ingredient Acetaminophen Fatality Reports (1996-2000 AAPCC reports)

Reason for exposure	Acetaminophen alone N	Acetaminophen + alcohol N	Total N	% of Total
Unknown	21	2	23	NA
Intentional unknown	11	1	12	6.3
Intentional suicide	88	10	98	51.6
Intentional misuse	33	12	45	23.7
Intentional abuse	2	2	4	2.1
Unintentional unknown (exact reason unknown)	3	0	3	1.6
Therapeutic error	20	7	27	14.2
Adverse reaction (adverse event occurred at recommended dose regardless of causality)	1	0	1	0.5

Discussion of Intentionality. When serious outcomes or death follow a drug overdose, intentionality is difficult to confidently determine. Spooner [1993] cautioned that coroners in the United Kingdom are reluctant to categorize a death as suicide unless there is hard evidence, such as a suicide note. In the absence of such evidence, accidental death is more likely to be the determined cause, even when there is strong suspicion of deliberate overdose. Physicians also may be reluctant to attribute self-harmful or suicidal intent if the patient is too ill to communicate or because of the impact on privacy, insurance coverage, or family relationships. Therefore, it seems likely that acetaminophen suicidal overdose intent is underreported in AAPCC fatality data.

Spooner also pointed out errors in attributing deaths to acetaminophen. Among 547 deaths in 1990 in England and Wales attributed to acetaminophen, only 27% were considered to be probably related. His assessment considered liver histopathology, identified causes other than liver necrosis, and the time course of death following acute suicidal ingestion. In the absence of similar close attention to clinical and pathologic details, the number of deaths causally attributed to acetaminophen, because of its incidental use in a large percentage of the population (23% in the past week), may be grossly exaggerated. The widespread prevalence of acetaminophen exposure and awareness that acetaminophen can produce hepatotoxicity (albeit at massive overdoses) may also contribute to misclassification by healthcare professionals of deaths as being acetaminophen related.

4.6.3.2 Selected Poison Control Center Data for Evaluating Pediatric Misadministration

Annual national AAPCC reports do not provide case details. To better understand the frequency, severity, and outcomes of pediatric acetaminophen misadministration, McNeil obtained 12 months of data (for the year 2000) from two regional AAPCC-certified poison centers (one in the west and one on the east coast) that serve large base populations. Together, the two centers received 3.4% of AAPCC exposure reports.

During 2000, these two centers received 74,417 calls of which 1730 calls reported exposure to an acetaminophen-containing product in children 0 to 11 years of age. Of these, 500 reports were coded as being therapeutic error, unintentional misuse, intentional misuse or intentional abuse. None reported a serious adverse outcome ("moderate" or "major" effect or "death"). Six reports were of children who received an acetaminophen dose in excess of the recommended daily dose of 75 mg/kg/day. Of these six reports, outcomes were classified as minor effects (3) and no effects (3). A majority of the reports (66.6%) involved scenarios where the caller contacted the poison control center for reassurance after realizing that they had mistakenly administered an incorrect dose or after they had inadvertently administered an acetaminophen-containing medication twice, 21% involved the administration of an inappropriate formulation or concentration, and 4% involved a single episode of concomitant administration of more than one acetaminophen-containing product.

Twenty-eight (28) of the 500 reports involved the use of the wrong dosing device to administer the acetaminophen-containing product. Twenty-one (21) of the 28 reports involved single-ingredient acetaminophen. Of these, 18 reports involved the ingestion of the concentrated acetaminophen drops formulation, of which 13 reports involved children less than two years of age for which dosing information is not presently permitted on the product label. None of these reports resulted in serious outcomes. The other three reports involved misadministration of children's liquid acetaminophen formulations; all of these reports involved children greater than two years of age. The remaining seven reports involved infants' (3) or children's (4) cough/cold products. Most of these reports involved mistaken use, and there were no serious outcomes.

From these data we conclude that pediatric misadministration rarely results in serious outcome. Rare events could be further prevented by permitting dosage information for children under two on the product label.

4.6.4 Drug Abuse Warning Network (DAWN)

To assess the nature of emergency department visits in the United States related to analgesic uses, data from the Drug Abuse Warning Network (DAWN) available online was used: http://www.samhsa.gov/oas/dawn.htm]. DAWN is an ongoing drug abuse data collection system sponsored by Substance Abuse & Mental Health Services Administration (SAMHSA) Office of Applied Studies. It collects data from: 1) hospital emergency departments and 2) medical examiners. The hospital emergency department component of DAWN relies mainly on a nationally representative sample of hospital emergency departments in 21 metropolitan areas to produce information on the number and characteristics of drug abuse-related visits to such hospital emergency departments in the United States.

An episode report is submitted to the DAWN system for each individual who visits a DAWN emergency department and meets **all** of the following criteria:

- The individual was age 6 to 97 and was treated in the hospital's emergency department;
- The presenting problem(s) (ie, the reason for the emergency department visit) was induced by or related to drug use, regardless of when the drug use occurred;
- The episode involved the use of an illegal drug or the use of a legal drug or other chemical substance for nonmedical purposes; and the reason for using the substance(s) was dependence, suicide attempt or gesture, and/or psychic effects.

In addition to drug overdoses, reportable emergency department episodes may result from the chronic effects of habitual drug use or from unexpected reactions. DAWN cases do **not** include accidental ingestion or inhalation of a substance with no intent of abuse, or adverse reactions to prescription or over-the-counter medications taken as prescribed.

The percentage of total drug-related episodes for various products containing either acetaminophen or NSAIDs for the year 2000 are provided in Table 4-9 in descending order. Drug-related episodes for OTC available NSAIDs, OTC acetaminophen, and prescription acetaminophen products accounted for 6.2%, 6.0% and 4.6% of the emergency room visits, respectively. This is an estimated percentage because patients could have experienced drug-related episodes after use of multiple drugs, and the actual percentages could be lower because each drug is reported separately.

Table 4-9. Percentage of Emergency Department Visits Associated with Analgesics Containing Either Acetaminophen or NSAIDs in the Year 2000 – DAWN data

Product	Percent of Total Drug-related Episodes
Acetaminophen	5.5
Ibuprofen	3.1
Acetaminophen-hydrocodone	2.9
Aspirin	1.8
Acetaminophen-oxycodone	1.1
Naproxen	0.8
Acetaminophen-codeine	0.6
Acetaminophen/ASA/caffeine	0.5

The 1997 DAWN data, the most recent available for downloading, were analyzed further. Of the 164,056 reports, 6,554 reported use of acetaminophen. Of the 6,544 acetaminophen exposures, 2,766 (42%) were reported to involve ingestion of single-ingredient acetaminophen (acetaminophen alone), while the rest involved acetaminophen plus other drugs (acetaminophen combination products or the coadministration of other drugs). The age distribution for these two groups was similar; 93.8% and 90.4% of the acetaminophen alone exposures and the acetaminophen plus other drugs exposures, respectively, were between the ages of 12 to 44.

The primary reason for presentation to the emergency department was drug overdose in 87.5% of the acetaminophen exposures and in 85.3% of the acetaminophen plus other drugs exposures. There were no reported deaths in the acetaminophen alone group and two reported deaths in the acetaminophen plus other drugs group. As shown in Table 4-10, suicide was the predominant motive for consumption of acetaminophen-containing products that resulted in hospital emergency department visits.

Table 4-10. Distribution of DAWN Reports by Drug Use Motive

Drug Use Motive	% of Total (Acetaminophen Alone Exposures)	% of Total (Acetaminophen + Other Drugs)
Suicide	77.1%	79.0%
Psychic Effects	14.0%	9.8%
Dependence	0.4%	2.7%
Recreational Use	0.9%	1.8%
Other	1.1%	0.7%
Missing	6.6%	5.9%

In summary, the frequency of hospital emergency department visits attributable to OTC available NSAIDs was similar to that of OTC acetaminophen. Suicide was the motive and

overdose was the reason for most emergency department visits that resulted from ingestion of acetaminophen-containing products. Death was rare.

4.6.5 Published Data On Liver Transplant Centers' Experience and Acute Liver Failure Registry

The most serious cases of acetaminophen hepatotoxicity may be referred to a hepatologist or liver transplant unit. As a result, these experts and centers see the most seriously ill patients. Experiences at two transplant centers have been published and are summarized in the following sections.

4.6.5.1 United Kingdom Experience

Makin [1995] retrospectively reviewed 560 medical records that indicated acetaminophen overdose during the period January 1, 1987 to December 31, 1993. Half (50%) of the patients reported taking an overdose after a financial, employment or personal event (eg, breakup of a relationship), 30% reported depression, and 38% reported at least one previous suicide attempt. Only 8% of the patients denied suicidal intent and reported an unintended overdose. Of those denying suicidal intent, 25% had a history of previous overdose attempt and 62% were heavy alcohol users; in these patients the median reported acetaminophen dose was 40 grams (range, 5 to 210 grams), with 71% taking more than 24 grams. Sixty-two percent (62%) of reportedly therapeutic overdoses were of more than 24 grams of acetaminophen; the authors reported that the acetaminophen dose was staggered over a number of hours or days. Forty-five (45) patients (8% of the 560 patients) alleged taking less then 12 grams, and none reported taking four grams or less. However, 35 (78%) of the 45 patients had a dose history of questionable reliability (17 had a history of deliberate acetaminophen overdose, eight were undergoing psychiatric treatment for depression, ten were consuming in excess of 40 units of alcohol per week, and five had serum acetaminophen concentrations that were inappropriately high for the alleged dose of acetaminophen taken). In addition, alcohol or anticonvulsant consumption did not affect overall clinical outcome.

4.6.5.2 Liver Failure Registry Experience

Lee and colleagues (the Acute Liver Failure Study Group) described their transplant case series to a varying degree in different sources. These sources include a review article [Lee 2001], an abstract and presentation at an FDA co-sponsored meeting (Drug-Induced Liver Disease: A National and Global Problem, February 12-13, 2001, Chantilly, VA) by Lee [FDA

2001], and in abstracts [Ostapowicz 2000; Larson 2000]. We have been unable to identify a peer-reviewed publication that provides a comprehensive and detailed description of the participating centers, data collection methods and findings. Further, requests to Dr. Lee for access to these data have been denied. Therefore, we have used the most comprehensive information from the FDA website and the Larson abstract in the following discussion.

These sources provide 203 cases of acute liver failure during approximately two years (January 1998 to April 2000). Of these, 79 cases (38%) were reported to be associated with acetaminophen overdose (27 reported taking acetaminophen-opiate prescription products); the overall survival rate among these patients was 72% (67% spontaneous survival and 6% received a liver transplant). Seventy-seven percent (77%) of these patients were female and the average age was 37 years. Sixty percent (60%) were classified as "accidental" overdose and 40% as suicidal overdose. The frequency of antidepressant use was similar between those who claimed suicidal overdose (35%) and those who claimed accidental overdose (37%). The prevalence of antidepressant use in the accidental overdose group was at least six times higher than expected since the percentage of United States adults who receive pharmacotherapy and/or psychotherapy for depression is 5.8% [Olfson 2002]. This suggests either that those who took antidepressants were more prone to "accidental" overdose, or perhaps, some of the "accidental" overdose cases were not truly unintentional. Given the prominent role of depression in suicidal overdose [McMahon 2001], one would not expect the frequency of antidepressant use in the two groups to be similar.

4.6.6 Conclusions Concerning Data Sources Available to Assess Misadministration and Overdose

The data sources we have used to assess the misadministration and overdose situations include spontaneous reports submitted to the FDA's Adverse Event Reporting System (AERS), poison control center reports, the Drug Abuse Warning Network (DAWN), and reports from liver transplant centers. These data sources are descriptive in nature and consist only of reports. In addition to our conclusions for AERS adult reports (Section 4.6.2.2.3, Conclusions from the FDA Selected AERS Data Set of Adult Reports), we conclude:

- Data from AAPCC, DAWN and liver transplant centers are consistent, and show that intentional suicide is the most frequent reason for adult acetaminophen overdose.

- Pediatric misadministration rarely results in serious outcome. Rare events could be further prevented by permitting dosage information for children under two on the product label.

4.7 Comparative Safety Analysis with NSAIDs

Acetaminophen is the most commonly used OTC analgesic and any actions that effectively limit its use, or the availability of optimal dosages that are currently available, may increase the use of OTC NSAIDs and prescription analgesics, among other pain and fever treatments. Comparing acetaminophen safety to that of aspirin and other NSAIDs at recommended doses suggests that an increase in aspirin and other NSAIDs use could increase the overall morbidity and mortality associated with therapeutic OTC analgesic use. The potential public health impact for the American consumer merits consideration.

For perspective, excess mortality from gastrointestinal bleeding, the factor that dominates the overall risk profile of NSAIDs, that occurs at recommended doses and is dose-related, is compared with excess mortality from hepatotoxicity from overdose with acetaminophen in the following sections.

4.7.1 Excess Mortality from Gastrointestinal Bleeding Associated with NSAIDs in the United States

The more common serious risks of aspirin and other NSAIDs are gastrointestinal bleeding, renal failure and congestive heart failure. Epidemiologic evidence suggests that 99% of the excess mortality from NSAID use is attributable to gastrointestinal complications [Report of CIOMS Working Group IV 1998]. Thus, the remaining discussion concerning NSAID risks in this section is limited to gastrointestinal complications.

The risk of gastrointestinal bleeding increases with NSAID dose [Blot 2000]. Blot and McLaughlin [Blot 2000] conducted an independent analysis of case-control data from a study conducted by the American College of Gastroenterology. The risk of gastrointestinal bleeding increased two to three-fold among recent users of aspirin, ibuprofen and other NSAIDs at OTC doses, and the risk was also dose-related. Additionally, Blot reviewed seven epidemiologic studies that looked at gastrointestinal bleeding risk associated with aspirin and other NSAIDs at OTC doses (eg, 3900 mg/day for aspirin and 1200 mg/day for ibuprofen) and reported about a two-fold excess risk of gastrointestinal complications at doses lower than the maximum recommended OTC dosage, with four-fold increases at

doses near the maximum, and an increase of six-fold or more at doses higher than recommended on OTC labels [Blot 2000].

Evaluation of NSAID risks should not be limited to OTC doses. Some consumers take more than the recommended daily doses of OTC NSAIDs [Havey 2001]. Singh [1999] noted that 40% of Americans (who had taken NSAIDs at least twice in the past year for five or more consecutive days) simultaneously used OTC and prescription NSAIDs. Based on consumer survey responses [Kaufman 2002], and taking into account concurrent use of two or more NSAIDs [Slone 2001], the one-week prevalence of aspirin and all other NSAID use is estimated as approximately 34%. This represents 71 million adults (0.34 x 209 million adults in the United States). Concurrent use of two or more NSAIDs was reported by 2.7% of all adults in the Slone Survey of Analgesic Use [Slone 2001]. Applying this rate to the adult population in the United States provides an estimate of up to 5.6 million adults who may concurrently use two or more NSAIDs. These concurrent users will be at higher risk for dose-related side effects.

Ofman and colleagues [2002] conducted an extensive meta-analysis of severe upper gastrointestinal complications from NSAIDs. They estimated the risk of upper gastrointestinal complications (perforations, ulcers and bleeds) using data from several study designs, concluding the findings from the cohort designs were the least biased. The pooled relative risk (RR) from nine cohort studies, comprising over 750,000 person-years of exposure was 2.7 (95% CI: 2.1, 3.5).

Singh [2000] estimated that 103,000 individuals are hospitalized annually in the United States for NSAID-related serious gastrointestinal complications at a cost in excess of two billion dollars. In addition, Singh [2000] estimated that 16,500 NSAID-related deaths occur each year in the United States among patients with rheumatoid arthritis and osteoarthritis.

A more conservative estimation came from Blot and McLaughlin (personal communication November 12, 2001) who estimated that 9,400 Americans, age 25 years or older, die from upper gastrointestinal bleeding per year. This is based on United States mortality data from the National Center for Health Statistics from 1990 through 1999[17].

[17] The ICD-9 codes used for calculating this estimate were 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, and 578.0 – 578.9.

Using the pooled relative risk of upper gastrointestinal bleeding from cohort studies determined by Ofman [Ofman 2002] of 2.7 (95% CI: 2.1, 3.5), McNeil estimated that the number of excess deaths per year from gastrointestinal bleeding secondary to NSAID use among adults in the United States is 3443 (95% CI; 2559, 4319). The point estimate of the number of excess deaths was calculated as follows. Estimates for the upper and lower 95% confidence interval were calculated in the same manner.

- Deaths per year attributable to NSAIDs in the United States
  = deaths per year from gastrointestinal bleeding (9400)
  x proportion attributable to NSAIDs (0.3662864)
  = 3443 deaths per year
- Proportion attributable to NSAIDs
  = $\frac{\text{prevalence of NSAID use (0.34) x [relative risk of GI bleed (2.7) – 1]}}{\text{prevalence of NSAID use (0.34) x [relative risk of GI bleed (2.7) – 1] + 1}}$
  = 0.3662864

Based on the Slone Survey of American adults [Kaufman 2002], the prevalence of use for acetaminophen was estimated to be 23%. Based on consumer survey responses [Kaufman 2002], and taking into account concurrent use of two or more NSAIDs [Slone 2001], the one-week prevalence of aspirin and all other NSAID use is estimated as approximately 34%. If half of OTC acetaminophen users switched to NSAIDs, this would increase the prevalence of NSAID use to 45.5% (34% plus 11.5%). Using the formulas provided above and an Excel spreadsheet, this would result in an estimated 4100 deaths per year due to gastrointestinal bleeding from NSAID use, ie, 657 additional deaths over the current estimate of 3443. If all acetaminophen users switched to NSAIDs, it is estimated that there would be 1183 additional deaths due to gastrointestinal bleeding from NSAID use, with a total of 4626 (Figure 4-1). Thus, for each percentage point switch of acetaminophen use (eg, from 23% to 22%, or from 1% to 0%) to aspirin or other NSAIDs, an additional 42 to 64 deaths due to gastrointestinal bleeding are projected. This concern is compounded by the fact that dyspeptic symptoms do not serve to warn of impending and serious gastrointestinal complications among patients taking NSAIDs. As many as 81% of patients who had serious gastrointestinal complications had no prior gastrointestinal symptoms [Singh 1996].

As the overall United States population ages, an increase in the prophylactic use of aspirin for cardiac protection is anticipated. Thus, more American adults will be exposed to aspirin and other NSAIDs concurrently. This combination could potentially increase the risk of

gastrointestinal bleeding due to the additional antiplatelet effect of aspirin. Concurrent use of aspirin with NSAIDs has been shown to increase the risk of gastrointestinal bleeding when compared with use of aspirin alone [Sorensen 2000].

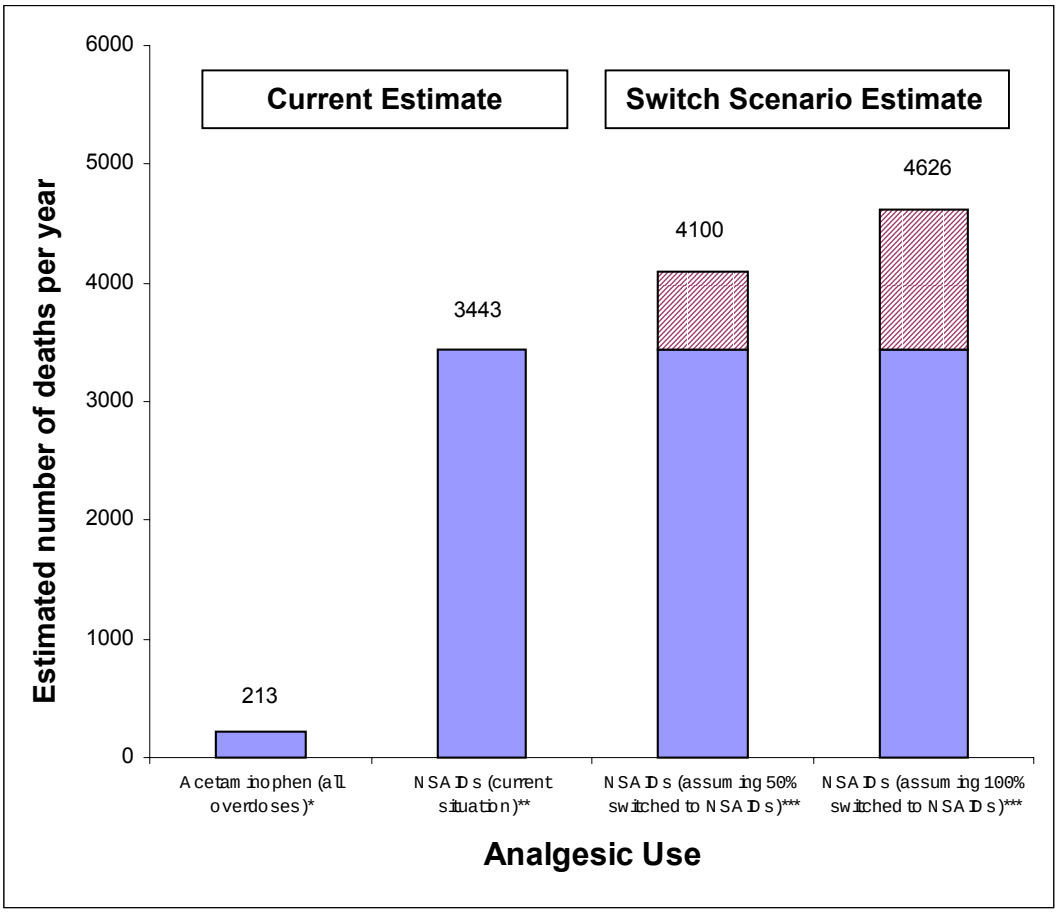
4.7.2 Excess Mortality Associated with Acetaminophen and Hepatotoxicity in the United States

Hepatotoxicity with acute liver failure following very large overdoses is the most prominent serious adverse event associated with acetaminophen. Although there are no surveillance programs or national statistics, one personal unverified estimate is that 2000 individuals develop acute liver failure annually in the United States, and 38% of cases may be attributable to acetaminophen [Lee 2001]. A 72% survival rate has been estimated [Larson 2000]. Little has been published about these cases so it is unclear how the attribution to acetaminophen was made or whether these estimates are accurate. However, in the absence of alternative estimates, McNeil used this information for a worst-case scenario of deaths from acetaminophen overdose: 213 per year (Figure 4-1).

4.7.3 Comparison of Excess Mortality

Figure 4-1 illustrates that the excess mortality from NSAID-related gastrointestinal bleeding at recommended doses far exceeds that from acute liver failure associated with acetaminophen overdoses. Even a modest shift from acetaminophen to aspirin or other NSAID use would be associated with a significant increase in the number of drug-related deaths.

Figure 4-1. Estimated Annual Excess Mortality Associated with Analgesic Use in the United States



* Personal unverified estimate of 2000 cases/year of acute liver failure, of which 38% (760) may be attributable to acetaminophen [Lee 2001]. A 72% survival rate has been estimated [Larson 2000]. 760 x 0.28 = 213.

** Estimated number of deaths per year attributable to NSAIDs in the US = deaths per year from upper GI bleeding (9400) x proportion attributable to NSAIDs (0.3662864) = 3443 deaths per year. The proportion attributable to NSAIDs was calculated as the {prevalence of NSAID use (0.34) x [relative risk of gastrointestinal bleed [Ofman 2002] (2.7) – 1]} divided by {prevalence of NSAID use (0.34) x [relative risk of GI bleed (2.7) – 1] + 1} which equals 0.3662864.

*** Prevalence of use for acetaminophen was estimated to be 23% [Kaufman 2002] and of NSAIDs to be 34% [Slone 2001]. If half of OTC acetaminophen users switched to NSAIDS, this would increase the prevalence of NSAID use to 45.5% (34% + 11.5%). This would result in an estimated 4100 deaths per year due to gastrointestinal bleeding from NSAID use, ie, 657 additional deaths over the current estimate of 3443. If all acetaminophen users switched to NSAIDs, it is estimated that there would be 1183 additional deaths due to gastrointestinal bleeding from NSAID use, with a total of 4626.

4.7.3.1 Comparison of Aspirin and Ibuprofen to Acetaminophen

Aspirin and ibuprofen are the two most commonly used NSAIDs in the United States. Using CIOMS estimation of mortality rates with short-term use [Report of CIOMS Working Group IV 1998] and the Slone Survey prevalence and use data for specific OTC NSAIDs [Kaufman 2002], one can estimate the number of deaths per year from gastrointestinal bleeding among short-term aspirin and ibuprofen users as 3013 and 795 (total of 3808), respectively. The total excess mortality (3808) from these two NSAIDs is comparable to the estimate (3443) for NSAIDs as a class as reported in Section 4.7.1, Excess Mortality from Gastrointestinal Bleeding Associated with NSAIDs in the United States.

4.7.4 Conclusion

In the choice of OTC analgesics, it is important to balance the therapeutic benefit against both the risk in therapeutic use, and the risk and available antidote treatment in overdose. Acetaminophen is the safest OTC analgesic at therapeutic doses. Massive acetaminophen overdose can lead to a high risk of hepatotoxicity, but the antidote NAC is widely available and prevents hepatic damage when administered early in the course. In contrast, serious adverse drug reactions occur more frequently with NSAIDs at therapeutic doses, are dose-related, and there is no antidote available for NSAID overdose.

The excess mortality from NSAID-related gastrointestinal bleeding at recommended doses (estimated as 3443 deaths per year) far exceeds that from acute liver failure associated with acetaminophen overdoses (estimated as 213 deaths per year). If acetaminophen use were to be restricted, and consequently aspirin and other OTC NSAID use increased in the United States, available data suggest that more people would die from aspirin and other NSAID-related gastrointestinal bleeding than those potentially spared from acetaminophen overdose hepatotoxicity.

Any change in the access or availability of any currently available OTC analgesics must be balanced against the risks presented by each of them. Consumers will self-treat pain and their selection of OTC analgesics will depend on the availability, accessibility, and effectiveness of these products.

5 CONSUMER MEDICATION USE

KEY POINTS

- Acetaminophen, ibuprofen, and aspirin are the most commonly used analgesic medications in the adult population of the United States. In any given week, some 23% of adults (48.1 million people) report using acetaminophen-containing products. The estimated prevalence of aspirin use is 17% and ibuprofen use is 17%. Naproxen use is 3.5% during this same time.

- Recent medication use surveys suggest that the vast majority of consumers use analgesics within the recommended OTC daily dose.

- Medication use surveys also provide insight regarding consumer analgesic use behaviors that may result in excessive OTC analgesic exposure.

- McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:
    - the product ingredients
    - the proper dosing and proper use of medications
    - the importance of not taking more than the recommended dose
    - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
    - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

5.1 Introduction

Acetaminophen-containing products are widely used throughout the United States. A recent survey of medication use in the United States estimated the some 23% of adults (48.1 million people) report taking acetaminophen-containing products in the preceding week [Kaufman 2002]. Information in this section demonstrates that consumers almost invariably take acetaminophen at the recommended OTC doses. As with any product available for direct use, acetaminophen can be misused. The misuse can be intentional or inadvertent. This section will examine recent data on consumer medication use behaviors and information regarding misuse of OTC analgesics. Based on this review, specific actions, directed at focusing the consumer on proper medication use, are discussed in Section 6, McNeil Initiatives and Recommendations.

5.2 Recent Sources of Information About Consumer Medication Use

5.2.1 Actual Consumer Medication Use

Slone Survey of Medication Use – an ongoing population-based telephone survey of medication use conducted by the Slone Epidemiology Unit (Slone) of Boston University School of Public Health [Kaufman 2002]. The survey provides recent information on use of all medications, including prescription and OTC drugs, vitamins and minerals, and herbal preparations/supplements during the 1-week period preceding a telephone interview. This survey represents a random sample of an ambulatory adult (18 years of age and older) population in the 48 continental states and the District of Columbia. As part of the interview, the participant is asked to gather the relevant bottles or packages on all medications taken during the preceding seven days.

At the request of McNeil, Slone conducted a specific analysis of utilization patterns of OTC and prescription analgesic products containing acetaminophen, aspirin, ibuprofen and naproxen based on the Survey of Medication Use. The supplemental analysis of analgesics includes a total of 6279 participants interviewed during the time period of February 1998 through August 2001. Herein, this analysis is referred to as “Slone Survey of Analgesic Use” [Slone 2001].

The MediScope^{SM} Household Survey – a diary-based survey of United States households demographically balanced to match US Census data provided by a market research service. Consumers are instructed to record every use of nonprescription medicine by all household members, regardless of age, for a four-week period. The data collected includes

the product name, the reason for using the product, the dose amount, and the number of doses taken. Survey data is available for approximately 6700 households over a two-year time period from September 1999 through September 2001 [McNeil 2002].

5.2.2 FDA-Selected AERS Data Set of Acetaminophen Reports

In Section 4, Assessment of Acetaminophen Safety, clusters of common factors are identified in spontaneously reported cases that have been submitted to the FDA Adverse Event Reporting System (AERS). FDA has identified a set of AERS reports with serious outcomes for the time period of January 1998 through March 2001 involving acetaminophen as a suspect drug. Only those reports with "hepatic" adverse event terms selected by the FDA were included. Of 306 reports in this data set, there were 281 adult (Section 4.6.2.1, FDA AERS Data Set – Adult Reports) and 25 pediatric (Section 4.6.2.2, FDA AERS Data Set – Pediatric Reports) case reports. These 306 reports are referred herein as the "FDA AERS Data Set".

5.2.3 Consumer Attitudes About Medications

McNeil Habits & Practices Survey – telephone survey of consumer attitudes and behavior regarding use of both OTC and prescription analgesic medications conducted by a market research service. A random sample of United States consumers was surveyed to identify OTC products they regularly use and their understanding of product ingredients and safety. The survey was conducted in September 2001 and sampled 410 male and female adults between the ages of 18 and 65 who had used OTC analgesics in the past six months [McNeil 2001].

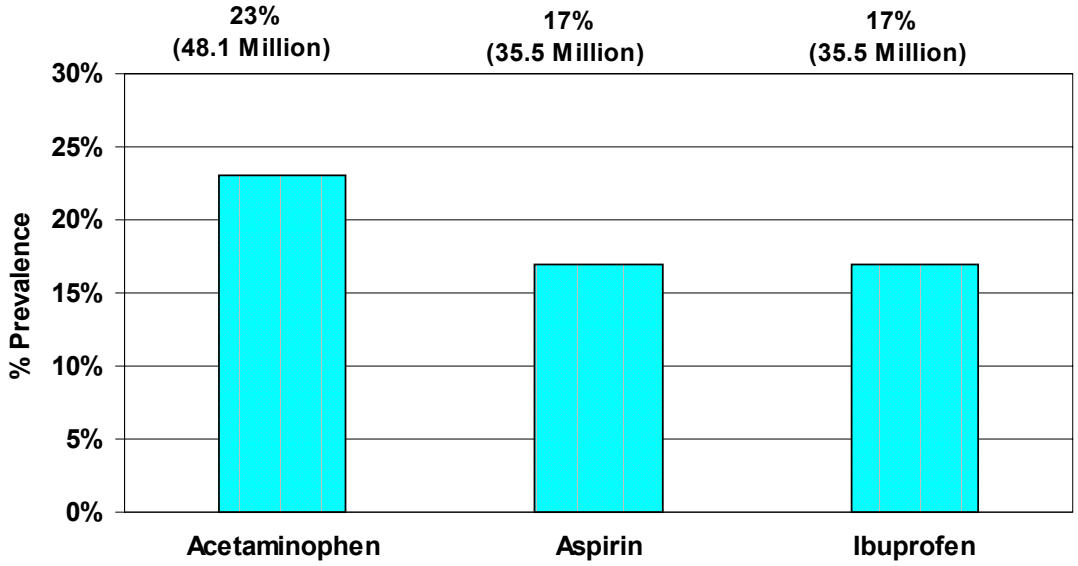
National Council on Patient Information and Education (NCPIE) Survey - a market research telephone survey of consumers and health professionals to track their opinions about the use of OTC medicines. The survey was conducted between October 25 and November 11, 2001 and consisted of two polls: one of 1011 adults 18 years of age and older and the other involving 451 pharmacists, nurses and general practice physicians. Interview questions focused on the general term of "non-prescription medicines", but did not specifically address the category of OTC pain relievers. Survey results were released to the public in January 2002 as part of the "Be Medwise" campaign [NCPIE 2002].

5.3 Patterns of Medication Use From Recent Sources

This section provides a description and perspective about patterns of use of OTC analgesics from recent sources.

According to the Slone Survey of Medication Use [Kaufman 2002], in the United States 61% of adults recall using some analgesic in the previous week. Some 23% of adults or 48.1 million people report using acetaminophen-containing products. The prevalence of aspirin use is 17% and ibuprofen use is 17%. These data are depicted in Figure 5-1. Naproxen use is 3.5% during this same time period.

Figure 5-1. One-Week Prevalence of Most Commonly Used Analgesic Products in the United States Adult Population (n= 209 million) From Slone Survey of Medication Use [Kaufman 2002]



5.3.1 MediScope™ Household Survey

The MediScope Household Survey provides additional detail about OTC medication use by adults. When the daily OTC analgesic tablet consumption by consumers is analyzed, the data in Table 5-1 show that the majority of consumers use analgesics within the recommended OTC dose. However, a small percentage of analgesic users exceed the recommended maximum daily dose; these usage rates are 1% for acetaminophen, 6% for ibuprofen, and 13.5% for naproxen sodium.

On days that individuals used acetaminophen, 99% of usage was 4000 mg (eight tablets) of acetaminophen or less per day. Another 0.9% of acetaminophen usage was between >4000 mg and up to 6000 mg per day. Very rarely do individuals report using more than 8000 mg acetaminophen daily.

For comparison, 94% of ibuprofen daily usage was of doses up to 1200 mg (six tablets), while 6% of daily usage exceeded 1200 mg (>6 tablets). Some 0.23% exceeded an ibuprofen dose of 2400 mg per day, while <0.03% exceeded the maximum prescription ibuprofen dose of 3200 mg per day.

For aspirin, 92.4% of daily usage was 1 to 2 tablets. These data may not represent typical consumer usage of aspirin for pain relief, since approximately 52% of reportage usage was for the prevention of heart attack or stroke, situations where low-strength aspirin is recommended.

For consumers who use naproxen sodium, daily doses of up to 660 mg (3 tablets) represent 86.5% of naproxen sodium use, while 13.5% reported exceeding the maximum OTC daily dose, with 1.9% of the total exceeded the prescription naproxen sodium dose of 1100 mg daily.

In summary, while the vast majority of analgesic usage by consumers is within the recommended OTC daily dose, a small percentage of consumers take substantially more that the recommended doses despite product labeling.

Table 5-1. Reported Distribution of Daily OTC Analgesic Tablet Consumption in an Average 4-Week Period Expressed as a Percentage of Usage Days (based on MediScope Household Survey Data from 9/99 – 9/01 [McNeil 2002])[a,b]

	Acetaminophen (8x - 500 mg tablets/day)[c,d]		Aspirin (500 mg tablet equivalent)[e]		Ibuprofen (6x – 200 mg tablets/day)[c]		Naproxen Sodium (3x – 220 mg tablets/day)[c]	
No. of Tablets	% Usage Days	Cumulative Usage %	% Usage Days	Cumulative Usage %	% Usage Days	Cumulative Usage %	% Usage Days	Cumulative Usage %
1	19.0	19.0	76.6	76.6	18.9	18.9	33.3	33.3
2	41.6	60.6	15.8	92.4	36.4	55.3	48.1	81.4
3	10.1	70.7	3.4	95.8	10.3	65.6	5.1	86.5
4	14.4	85.1	2.8	98.6	18.5	84.1	**11.5**	**98.0**
5	1.2	86.3	0.3	98.9	1.2	85.3	**0.1**	**98.1**
6	8.2	94.5	0.7	99.6	8.7	94.0	**1.3**	**99.4**
7	0.6	95.1	0.1	99.6	**0.6**	**94.6**	**0.1**	**99.5**
8	3.8	99.0	0.3	99.9	**2.4**	**97.0**	**0.3**	**99.8**
9 to 12	**0.9**	**99.9**	0.1	100.0	**2.7**	**99.7**	**---**	**99.8**
13 to 16	**0.1**	**99.9**	0	100.0	**0.2**	**99.0**	**---**	**99.8**
17 to 20	**<0.1**	**100.0**	0	100.0	**0.03**	**100.0**	**0.2**	**100.0**
% days > max. daily OTC analgesic dose	**1.0**	**---**	Not applicable since use not only for pain relief	--	**6.0**	**---**	**13.5**	**---**

a: Adult single-ingredient analgesic preparations (including PM product) among users 12 years of age and older.
b: Bold indicates usage days exceeding the recommended maximum daily OTC analgesic dose.
c: Total number of tablets/day to equal the recommended maximum daily OTC analgesic dose.
d: Actual mg usage (based upon intake of 325, 500, or 625 mg) standardized to 500-mg tablet.
e: Actual mg usage (based upon intake of 325 or 500 mg) standardized to 500-mg tablet.

5.3.2 Slone Survey of Analgesic Use

In this survey, 81% of acetaminophen users reported taking one OTC acetaminophen product and 11% reported taking one prescription product containing acetaminophen [Slone 2001]. Of all acetaminophen users, 75% identified a specific acetaminophen dose and 25% reported an unknown dose. Of those who reported a dose, ninety-nine percent (99%) reported a dose of no more than the maximum OTC recommended daily acetaminophen dose of 4000 mg, whereas, 1% reported taking more than 4000 mg daily. A somewhat higher percentage, 13%, of all ibuprofen users reported a dose of more than the maximum recommended OTC dose of 1200 mg per day, and 1% reported taking more than 3200 mg daily. Comparable survey information for naproxen was not collected [Slone 2001].

Regarding aspirin, 79% of all users of aspirin reported using a single-ingredient product. A large group (41%) of aspirin users reported a daily dose of 325 mg or less with a median duration of use of three years. This long duration is consistent with cardiovascular prophylaxis being the most frequently reported reason for aspirin use (48%). Another aspect of the aspirin usage was a pattern of its concurrent use with other NSAIDs. Aspirin was used concurrently with ibuprofen, naproxen, or ibuprofen plus naproxen by a total 2.5% of subjects in the survey.

The Slone Survey also provides additional insight regarding the use of other types of acetaminophen-containing products by consumers. Low percentages of acetaminophen users reported combined use of a single-ingredient OTC acetaminophen product with either an OTC acetaminophen containing combination (5%) or a prescription acetaminophen-containing combination (2%).

A small fraction of OTC analgesic use is greater than the recommended dose. Table 5-2 provides a summary of the reported average daily acetaminophen exposure by type of OTC or prescription (Rx) acetaminophen product taken by consumers. In this survey a single individual reported taking more than the recommended dose of acetaminophen from among those who used only one OTC single-ingredient acetaminophen product. Among individuals taking only one Rx acetaminophen-containing analgesic, two reported taking from 4001 mg to up to 8000 mg per day and one reported taking more than 8000 mg daily. However, in this category of prescription products a high proportion (49%) of unknown dose was reported [Slone 2001].

When two OTC products containing acetaminophen were being used, 5% reported taking more than 4000 mg to 6000 mg and 3% reported taking more than 6000 mg to 8000 mg. When taking both an Rx and an OTC analgesic containing acetaminophen, 3% reported taking more than 4000 mg daily. For all users of two products containing acetaminophen, no individuals reported using more than 8000 mg per day of acetaminophen. Users of two acetaminophen-containing type products reported high proportions, 42% and 47%, of unknown dose.

Table 5-2. Average Daily Acetaminophen Exposure (mg) by Type of Acetaminophen Product Taken (Slone Survey of Analgesic Use) [Slone 2001]

Daily Acetaminophen Exposure (mg)	- - - - - % of Product Category Taking Dose Within the Stated Range - - - - -				
	Use of One Product Only			Use of Two Products	
	OTC Single-ingredient (n=720)[a]	OTC Combination (n=405)	Rx (n=158)	OTC plus OTC combination (n=65)	Rx plus OTC products (n=30)
Less than 2000	72%	85%	43%	37%	27%
2001 to 4000[b]	4%	3%	6%	14%	23%
4001 to 6000	0.1%	0%	1%	5%	0%
6001 to 8000	0%	0%	0%	3%	3%
More than 8000	0%	0%	0.6%	0%	0%
Unknown dose	24%	12%	49%	42%[c]	47%

a: Total number of users within the specified category
b: Maximum recommended daily OTC analgesic dose
c: One subject reported using more than 4000 mg daily (actual dose not specified)

5.3.3 FDA-Selected AERS Data Set

Case reports are limited by their anecdotal and retrospective nature. For acetaminophen and hepatic events, the majority of reports contained in the AERS database are overdose cases. Section 4.6, Data Sources Available to Assess Misadministration and Overdose, describes some clusters of common factors in the FDA selected AERS data set of 307 cases. Of the adult reports, these common factors involve taking more than the recommended dose, either by exceeding the recommended daily dose of single-ingredient acetaminophen products or by taking multiple acetaminophen-containing medications.

The majority of the pediatric case reports involved situations where the child was given substantial overdoses of a single ingredient pediatric acetaminophen product. Most of these reports involve children less than two years of age for which dosing is not permitted on the OTC package label.

5.4 Assessment of Consumer Medication Use

Labels of OTC medications contain adequate information for safe use of a product when read and followed by a consumer. Yet reports of consumer misuse are available. McNeil is not aware of any definitive studies that examine the association between consumer medication use behaviors and increased risk, but it seems possible that some reported consumer practices, described below (in bold), may be reduced with labeling changes and dissemination of more widespread and pervasive consumer and healthcare professional education programs.

When using single-ingredient OTC analgesic products -- consumers may ingest amounts that exceed recommended dosing.

Review of recent data suggest possible reasons for this behavior:

- Pain may be so severe that extra medicine was taken for relief
- Not understanding that two products containing the same analgesic (acetaminophen or NSAID) should not be taken together in a higher than recommended single or daily dose
- Failure to read dosing instructions and warnings
- Failure to heed label warnings
- Not believing that harm could occur from taking too much medication, despite warning language
- Ingestion of alcohol or other substances that impair reasoning or judgment
- Intentional self-harm.

Even though actual medication use data indicated that excess use over the maximum daily dose is rare, in the McNeil Habits and Practices Survey 23% of consumers reported usually taking more than the OTC recommended single dose when taking the <u>first</u> dose of a non-prescription pain reliever. Of these respondents, the most frequent reasons why they usually take more than the recommended single dose were reported as “have multiple symptoms” (49%), “want faster relief” (19%), “have severe pain” (11%) and “told by doctor” (10%).

Similarly, among NCPIE survey respondents asked about taking more than the recommended dose of a non-prescription medicine, 33% recalled having ever taken more than the recommended dose. Sixty-eight percent (68%) of the respondents, who recalled

ever taking more than the recommended dose, reported doing so because they had severe symptoms.

In the McNeil OTC Habits and Practices survey, when consumers reported using two OTC products containing the same pain reliever, they were asked why they were not concerned about this practice. Some of their responses suggest that they thought it was safe to do so: "It's safe because it is the same medicine" (27%); "I never experienced side effects" (14%), "it's safe to take together" (8%); or "OTCs are not strong enough" (5%) [McNeil 2001]. However, when asked in the survey if they think any adverse effects are possible if more than the recommended dose is used on a regular basis, 88% said that they believed adverse side effects are possible.

These responses require cautious interpretation since they may reflect a lack of concern by consumers regarding a one-time or occasional use beyond the recommended dose.

When using prescription pain relievers containing acetaminophen plus single-ingredient OTC acetaminophen products -- consumers taking both products at the same time may take enough acetaminophen to exceed the currently recommended total daily dose.

Review of recent data suggest possible reasons for this behavior:

- Severe pain states causing consumers to take additional pain relievers to relieve residual pain
- Not knowing that either the prescription pain reliever or both pain relievers contain the same active ingredient
- Not understanding that products containing the same active ingredient should not be taken simultaneously to avoid exceeding the maximum recommended single or daily dose.
- Abusive use patterns in the intake of one or more pain relievers
- Intentional self-harm.

The McNeil Habits and Practices Survey provides relevant data. This survey demonstrates that consumers did not know or could not recall what certain prescription products contained. Only one of 61 consumers who were taking Vicodin®, Percocet®, or Endocet® knew that the product contained acetaminophen. None knew what the other active

ingredient was in any of these products. Reasons reported by respondents who reported taking a prescription pain reliever and some other type of non-prescription pain reliever at the same time included, “symptoms not relieved” (26%), “have multiple symptoms” (21%), “have severe symptoms” (19%) and “told by doctor to take multiple products” (17%).

When using OTC combination (cough/cold) products plus single-ingredient OTC pain reliever products containing the same analgesic (acetaminophen or NSAID) -- consumers may take two (or more) OTC products for multiple symptoms, thus taking increased doses of some ingredients.

Review of recent data suggest possible reasons for this behavior:

- Not recognizing that some multi-symptom relief products contain a pain reliever
- Not recognizing the risk of taking two products containing the same active ingredient (acetaminophen or NSAID).

The McNeil Habits and Practices survey provides insight regarding these behaviors. Respondents generally were not aware that cough/cold products also contained an analgesic. Specifically, 66% of consumers knew that Tylenol Cold®, 47% knew Vick’s Nyquil®, 40% knew Alka-Seltzer Plus Cold®, and 35% knew Sudafed Cold & Cough®, respectively, contained a pain-relief ingredient (acetaminophen). For ibuprofen-containing products 69% knew that Motrin® Sinus/Headache and 62% knew that Advil® Cold & Flu contained a pain-relief ingredient. It appears that using the tradename of an analgesic (eg Tylenol or Motrin) within the name of a combination product increases consumer awareness of the analgesic component of these combination products.

Again, some respondents in the Habits and Practices survey expressed a lack of concern when taking two OTC products if they knew the two products contained the same pain reliever. When queried, the most frequent responses included: “It’s safe because it is the same medicine” (27%); “I never experienced side effects” (14%), “it’s safe to take together” (8%); or “OTCs are not strong enough” (5%). The survey did not include questions specifically addressing consumer attitudes about exceeding the maximum daily dose. However, 88% of respondents agreed that adverse side effects were possible if more than the recommended dose of an OTC pain reliever were used on a regular basis. Again, cautious interpretation is warranted because a perception of “safe” may relate to one time use.

When using pediatric products – caregivers may not adhere to or access proper dosing directions

Information from review of recent sources suggest some reasons for this behavior:

- Lack of clarity about dosage for children under two years of age
- Giving an adult dose to a child
- Confusion regarding pediatric dosage forms
- Extra, possibly inadvertent, dosing by multiple caregivers.

In the McNeil Habits and Practices Survey, when parents of children under the age of 12 years were asked if they ever gave a child an adult medicine, 17% responded "yes". Of those who reported giving a child an adult formulation, 19% followed a doctor's instruction and 26% used the dosing instructions for children on the label or used a lower dose.

Some parents (30%) of children less than two years of age reported having difficulty determining what the correct dose should be when giving a pain reliever or fever reducer product to their child. They reported calling their doctor (67%) or consulting a doctor's reference chart (6%) or another health professional (8%) to determine the correct dose [McNeil 2001]. This information suggests that, in most cases, precautions are taken by consumers to administer an appropriate dose to children.

5.5 Conclusions

Recent medication use surveys suggest that the vast majority of consumers use analgesics analgesic use within the recommended OTC daily dose. They also provide insight regarding consumer analgesic use behaviors that may result in excessive OTC analgesic exposure.

McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:

- the product ingredients
- the proper dosing and proper use of medications
- the importance of not taking more than the recommended dose
- the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
- the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

6 MCNEIL INITIATIVES AND RECOMMENDATIONS

KEY POINTS

- Based on review of surveys regarding consumer behaviors and other available data regarding misuse of OTC analgesics, McNeil proposes that labeling and educational interventions for enhancing proper consumer behaviors should be aimed at focusing the attention of all OTC medication users on:
  - the product ingredients
  - the proper dosing and proper use of medications
  - the importance of not taking more than the recommended dose
  - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
  - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.
- Medication use surveys provide insight to formulate risk management initiatives to reduce excessive OTC analgesic exposure.
- Prior McNeil initiatives include introduction of tamper-resistant product formulations and packaging, an educational program for Children's Tylenol products, development of the SAFE-TY-LOCK integrated dropper and bottle for Infants' Tylenol Concentrated Suspension Drops, and voluntary compliance with FDA proposed rules (Alcohol Warning and Drug Facts Labeling) in advance of the Final Rules.
- Prior McNeil requests pending at FDA include a Citizen's Petition filed with the agency in 1999 to expand dosing directions on OTC pediatric acetaminophen product labeling to include children under two years of age.

- McNeil has implemented labeling and educational interventions aimed at focusing the attention of OTC medication users on:
  - the product ingredients
  - the proper dosing and proper use of medications
  - the importance of not taking more than the recommended dose
  - the importance of not using two products containing identical ingredients or using the same class of analgesic ingredients (eg, NSAIDs) during the same period of time
  - the importance of recognizing that all medications have risks, particularly when more than the recommended dose is taken.

- McNeil is also sponsoring an ongoing survey of consumer behaviors to monitor changes in consumer OTC analgesic use behaviors.

6.1 Introduction

Medication use surveys provide insight regarding consumer behaviors that may result in excessive OTC analgesic exposure. These behaviors affect the use of:

- OTC single-ingredient adult analgesic products;
- Prescription pain relievers with single-ingredient OTC analgesics;
- OTC combination (cough/cold) products plus single-ingredient OTC analgesics;
- OTC pediatric analgesics (administered by parents to their children).

In this section, we describe previous and recently implemented interventions to promote the safe use of OTC analgesics in general, and acetaminophen in particular to help reduce the occurrence of excessive OTC analgesic exposure or overdose.

6.2 McNeil's Previous Initiatives

6.2.1 Chronology of Previous Initiatives

In an effort to promote the safe and appropriate use of OTC medicines, McNeil:

- Initiated the N-acetylcysteine (NAC) IND for the treatment of acetaminophen overdose (1978).
- Funded support for Rocky Mountain Poison Center to handle calls related to acetaminophen overdose (1979 to present).
- Provided detailed acetaminophen overdose management guidelines; including fundamental information published in Physicians' Desk Reference (1979 to present) and more detailed information in the Guidelines for the Management of Acute Acetaminophen Overdose (1979 to present).
- Developed tamper-evident packaging (1982).
- Funded support for the development of NAC, for the treatment of acetaminophen overdose (1985).
- Replaced capsules with a tamper-resistant caplet formulation in response to product tampering (1986).
- Voluntarily added a concomitant use statement to the Warnings section of acetaminophen labeling (1994).
- Voluntarily added the proposed alcohol warning to all Tylenol products in 1994 in advance of the final rule published in 1998.

- Initiated an education program for Children's Tylenol products, focusing on the use of the proper dosage device (1997).
- Implemented an easier to read format on Tylenol labeling (1998) in advance of the **Drug Facts** final rule (1999).
- Introduced the SAFE-TY-LOCK system for Infants' Tylenol Suspension Drops to promote proper administration of infants' concentrated acetaminophen drops (1999).

An example of a successful McNeil-initiated intervention and ongoing monitoring program is presented below for infants' acetaminophen concentrated drops.

6.2.2 Previous Initiatives: Programs to Reduce Misadministration of Pediatric Acetaminophen Products

Liquid single-ingredient acetaminophen products are available in two concentrations. For children at least two years old, products are formulated to contain acetaminophen at a concentration of 160 mg per 5 mL. For infants, a concentrated suspension drops product contains acetaminophen, 80 mg/0.8mL, to provide medication in a volume suitable for infants.

Based on a few manufacturer reports of parents using a dosing device other than the enclosed dropper to administer acetaminophen infants' concentrated drops, McNeil has instituted several interventions. These include dosing instructions, revised labeling, and an integrated dropper system.

Dosing Instruction

In 1983, McNeil developed acetaminophen-dosing schedules based on age and weight, to supplement the labeling instructions as published in the 1977 proposed rule [Temple 1983]. These schedules were made available to healthcare professionals through the Physicians' Desk Reference (PDR) and through professional materials. McNeil submitted in 1999 a Citizen's Petition to the FDA requesting an expansion of the OTC labeling of pediatric acetaminophen products to include dosing instructions for children under two years of age (down to two months of age for infants' drops and to four months of age for children's liquids) to make the information available to all consumers. Additionally, as of an August 2002 (report on file) survey, 84% of pediatricians believe that dosing for children less than 2-years-old should be provided on the label of the infants' drops products.

Revised Labeling

In 1997, McNeil added the words “concentrated drops” to our infants’ drops labeling to highlight the difference between the drops and other children’s products. The warning section was revised to include the statements, “Do not exceed recommended dose. Taking more than the recommended dose (overdose) may not provide more pain or fever relief and could cause serious health problems.” There was also an increased emphasis on the importance of using the proper dosing device (included in the package).

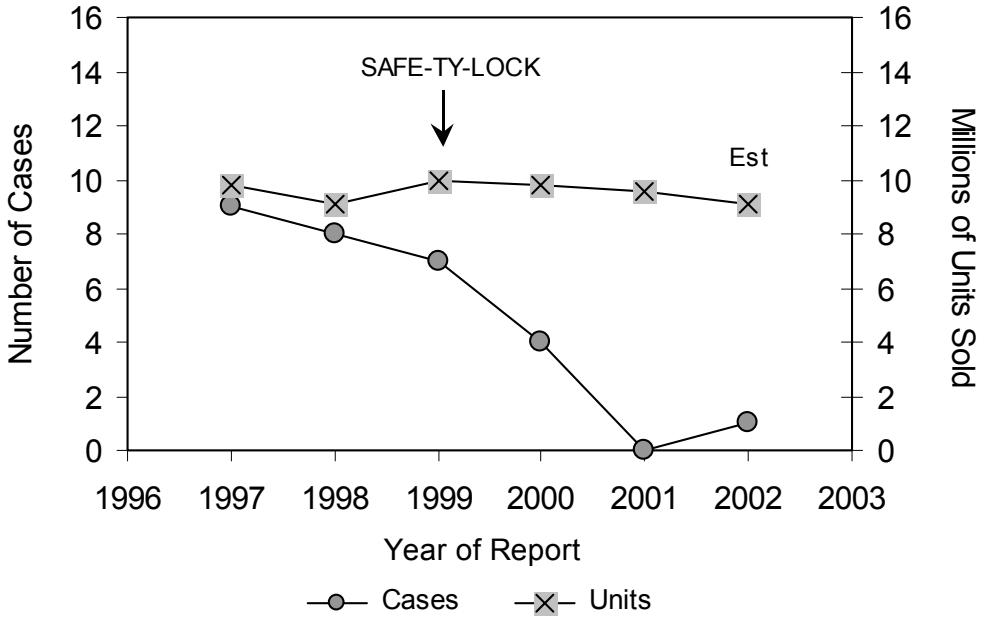
Integrated Dropper System

In 1999, McNeil introduced the SAFE-TY-LOCK, with its unique safety barrier inside the bottle designed to prevent pouring the concentrated infants’ drops product out of the bottle. The barrier works for suspension formulations because they are viscous. This design reduces the risk of misadministration that results from using a dosing device other than the provided dropper and also makes it difficult for a child to accidentally ingest medicine from an open, unattended bottle.

After the introduction of the SAFE-TY-LOCK in 1999, the number of misadministration cases associated with the infants’ concentrated drops product reported to McNeil declined notably (Figure 6-2). In 1998, McNeil received eight reports of misadministration associated with the use of the infants’ concentrated drops product. The number of reports has steadily declined after the introduction of the SAFE-TY-LOCK. There were no reported cases in 2001 and a single report in the first quarter 2002 for which little information has been provided except that released by the media. McNeil continues its efforts to obtain additional understanding of the details surrounding this report.

These initiatives related to the infants’ concentrated drops products facilitate the safe use of the product that is integral to the treatment of pain and fever in young children. An August 2002 survey (report on file) indicates that 86% of pediatricians state that acetaminophen concentrated drops are the preferred product for infants (6 months of age) with a fever.

Figure 6-2. Acetaminophen Concentrated Suspension Drops Misadministration Cases Reported to McNeil



6.3 McNeil's Current Initiatives

6.3.1 McNeil OTC Analgesic Product Labeling Initiatives

Appropriate consumer medication use requires knowledge of the safe and effective dose, as well as adherence to labeled contraindications to use, warnings about use in special circumstances, and directions when ingestion exceeds the recommended dose. McNeil's current acetaminophen labeling explicitly warns consumers against concurrent use of multiple acetaminophen-containing products, warns against taking an overdose, and provides instructions in the event of accidental overdose.

Despite these efforts, some consumers may not be aware of the specific active ingredient contained in OTC single-ingredient or combination-ingredient analgesics. Results from the McNeil Habits and Practices survey [McNeil 2001] indicate that respondents generally were not aware that cough/cold products also contained an analgesic. In addition, some consumers may not be aware or may disregard the maximum recommended single-dose or maximum recommended total daily dose. According to results from the McNeil Consumer Habits and Practices Survey, respondents were not concerned about this practice. These

responses require cautious interpretation since they may reflect a lack of concern by consumers regarding a one-time or occasional use beyond the recommended dose.

Consequently, McNeil has revised its product labeling to direct the attention and enhance awareness of consumers to key label information that may reduce the occurrence of excessive acetaminophen exposure. Revisions are being implemented for McNeil's monograph single-ingredient and cough/cold-combination products containing acetaminophen. McNeil has also requested revisions to the labeling for its NDA single-ingredient pain relievers. In addition, McNeil has worked with in-pharmacy prescription label producers to revise labeling on all prescription products that contain acetaminophen. These efforts are described below.

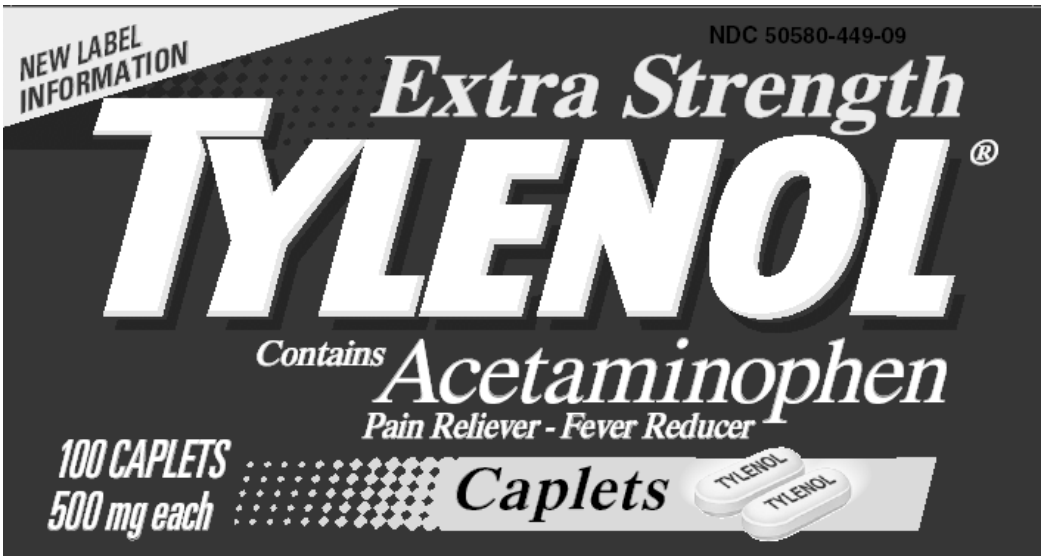
6.3.1.1 Monograph Labeling of OTC Single-Ingredient and Combination Products

Specific labeling revisions include those of language and format that stress key information. These revisions will appear on cartons, bottle labels, and blister cards.

Revisions to packaging include changes that are not currently required by FDA regulation. The changes include: 1) increasing the type size of active ingredient(s) on the principal display panel for all single-ingredient products; 2) adding active ingredient names to the principal display panel for all cough/cold-combination products; and 3) presenting the first letter of the name of active ingredient(s) in upper case type with the remainder in lower case type. These revisions are illustrated in the package examples that follow.

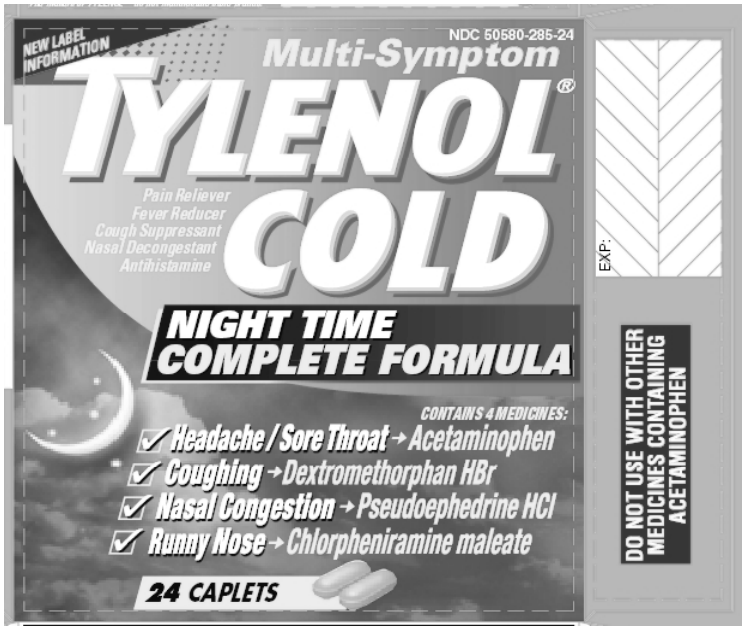
Previous Labeling for Tylenol® –Principal Display Panel of Carton

New Labeling –Principal Display Panel of Carton: Increased Prominence of Active Ingredient and Addition of Flag (upper left)



Previous Labeling Tylenol® Cold –Principal Display Panel of Carton

New Labeling –Principal Display Panel of Carton: Active Ingredients Prominently Displayed with Concomitant Use Statement on Side of Box



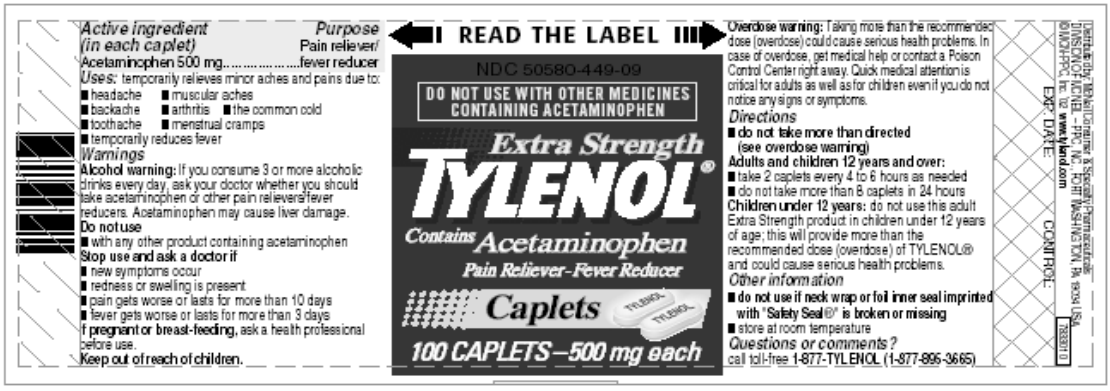
Revisions to the back panel (or **Drug Facts**) are not shown and include highlighting the active ingredient(s), creation of a distinct **Overdose warning** section that is separated from the "Keep out of reach of children" statement and reference to the **Overdose warning** in the **Directions** section of the labeling. The **Overdose warning** reads as follows:

> **Overdose warning:** Taking more than the recommended dose (overdose) could cause serious health problems. In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms.

Revisions to the bottle label on Tylenol® brand products also include a prominently displayed concomitant use warning, a more prominent active ingredients listing on the front principal display panel, and at the top of the principal display panel near the lid - a "Read The Label" message. An example of the bottle label revisions is presented below:

Previous Tylenol® Labeling – Bottle

New Labeling – Bottle: Addition of Concomitant Use Warning, Increased Prominence of Active Ingredients, Added "Read The Label" Message



A detailed summary of the specific labeling revisions being made to the outer carton and bottle label of monograph single-ingredient acetaminophen products is provided in Table 6-1. Table 6-2 provides a summary of revisions relevant to cough/cold-combination products containing acetaminophen.

Table 6-1. Summary of McNeil OTC Labeling Revisions Implemented for Tylenol® Brand Single-Ingredient Products Marketed under the Monograph System

Labeling Revisions
Outer carton and bottle label: • Increased type size and prominence of the active ingredient on the PDP* and added the word "contains" before the ingredient. • Presented the first letter of the active ingredient name in upper case type with the remainder in lower case type. • Highlighted the ***Active ingredient*** section of the ***Drug Facts*** box (carton) and the bottle label in yellow contrasting color. • Created a distinct **Overdose warning** section, separating it from "**Keep out of reach of children**" and revised the existing overdose warning language: **Overdose warning**: Taking more than the recommended dose (overdose) could cause serious health problems. In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. • Added to the ***Directions*** section of both the ***Drug Facts*** box (carton) and bottle label: "**do not take more than directed (see overdose warning)**"
Outer carton only: • Added a flag "NEW LABEL INFORMATION" to the upper corner of the PDP in contrasting color that will be included for a minimum of 6 months.
Bottle label only: • Added "DO NOT USE WITH OTHER MEDICINES CONTAINING ACETAMINOPHEN" to the PDP. • Added "READ THE LABEL" to the PDP.

Abbreviations: PDP = principal display panel.

Table 6-2. Summary of McNeil OTC Labeling Revisions Implemented for Tylenol® Brand Cough/Cold-Combination Products Marketed under the Monograph System

Labeling Revisions
Outer carton: • Added active ingredient names to the PDP* in prominent type size, with the first letter of the ingredient in upper case type and the remainder in lower case type. • Added "contains (number of) ingredients" to the PDP. • Created a distinct **Overdose warning** section, separating it from "**Keep out of reach of children**" and revised the existing overdose warning language: **Overdose warning:** Taking more than the recommended dose (overdose) could cause serious health problems. In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs or symptoms. • Added to the ***Directions*** section of the ***Drug Facts*** box in bold type: **"do not take more than directed (see overdose warning)"** • Added a flag "NEW LABEL INFORMATION" to the upper corner of the PDP in contrasting color that will be included for a minimum of 6 months. • Added "DO NOT USE WITH OTHER MEDICINES CONTAINING ACETAMINOPHEN" on the side flap of the box opened by the consumer and added "OPEN FROM OTHER SIDE" on the opposite flap of the box. • Highlighted the ***Active ingredient*** section of the ***Drug Facts*** box (carton) in yellow contrasting color. Blister cards: • Added "CONTAINS ACETAMINOPHEN" to all blister cards.

Abbreviations: PDP = principal display panel.

6.3.1.2 Labeling of Prescription Acetaminophen-Containing Products

The McNeil Habits and Practices Survey indicates that consumers did not know or could not recall what certain prescription analgesic products contained. Only one of 61 consumers who were taking Vicodin®, Percocet®, or Endocet® knew that the product

contained acetaminophen. None knew what the other active ingredient was in any on these products. We hypothesize that excessive acetaminophen exposure can occur with prescription products if individuals are not aware that acetaminophen is present in their prescription analgesic product. Additionally, despite information on current OTC labels, some consumers may not be aware or may disregard the potential for acetaminophen overdose when taking concomitant OTC and prescription products containing acetaminophen.

To address these issues, McNeil sought to revise the labeling information provided on prescription products containing acetaminophen. McNeil identified one of the major companies that provides drug label database services to most of the pharmacy market, including several of the largest chains and has advised them of the rationale for revising labeling on all prescription acetaminophen-containing products. Based on this information, beginning March 11, 2002, the company independently created and added to the labeling database two new auxiliary warning labels (ie, those labels placed directly on prescription bottles) specific to acetaminophen:

- This medicine contains ACETAMINOPHEN. Taking more ACETAMINOPHEN than recommended may cause serious liver problems.

- Do not take other ACETAMINOPHEN containing products at the same time without first checking with your Doctor. Check all medicine labels carefully.

An additional revision has been implemented, that specifically spells out “acetaminophen” instead of using an abbreviation. For example, the generic name “codeine phosphate/APAP” is now printed as “codeine phosphate/acetaminophen” on the bottle label.

These revisions are being introduced throughout the United States. All pharmacies using this label database service will have the new revisions in place by the end of 2002.

6.3.2 Consumer and Healthcare Professional Education Initiatives

Some consumers may not be aware of the specific active ingredient contained in single-ingredient analgesics. To highlight the proper use of OTC analgesics, maximize compliance with labeling recommendations, enhance understanding of the medications consumers are using, and to caution against the use of multiple analgesics, McNeil has instituted or participated in several consumer education initiatives.

6.3.2.1 Education Targeting Consumers: McNeil's "Know Your Medicine" Initiative

In March 2002, McNeil launched its "Know Your Medicine" campaign to complement another major campaign developed by the National Council on Patient Information and Education (NCPIE, described below). This initiative seeks to encourage proper dosing and awareness of OTC analgesic products using three key messages:

- Read the label
- Know what's in your medicine
- Count the doses.

Consumer "touch points" for delivery of these key messages include print and radio advertising, direct mail, retail outlets, the Internet, pharmacies, and doctors' offices. Key education partners in the McNeil "Know Your Medicine" initiative include the American Academy of Family Physicians (AAFP) and the American Pharmacist Association (APhA), in addition to the NCPIE. McNeil is currently identifying additional potential partnership opportunities, including other OTC manufacturers, retailers, and third party professional organizations to further help educate consumers.

Examples of specific activities related to the "Know Your Medicine" initiative include the following:

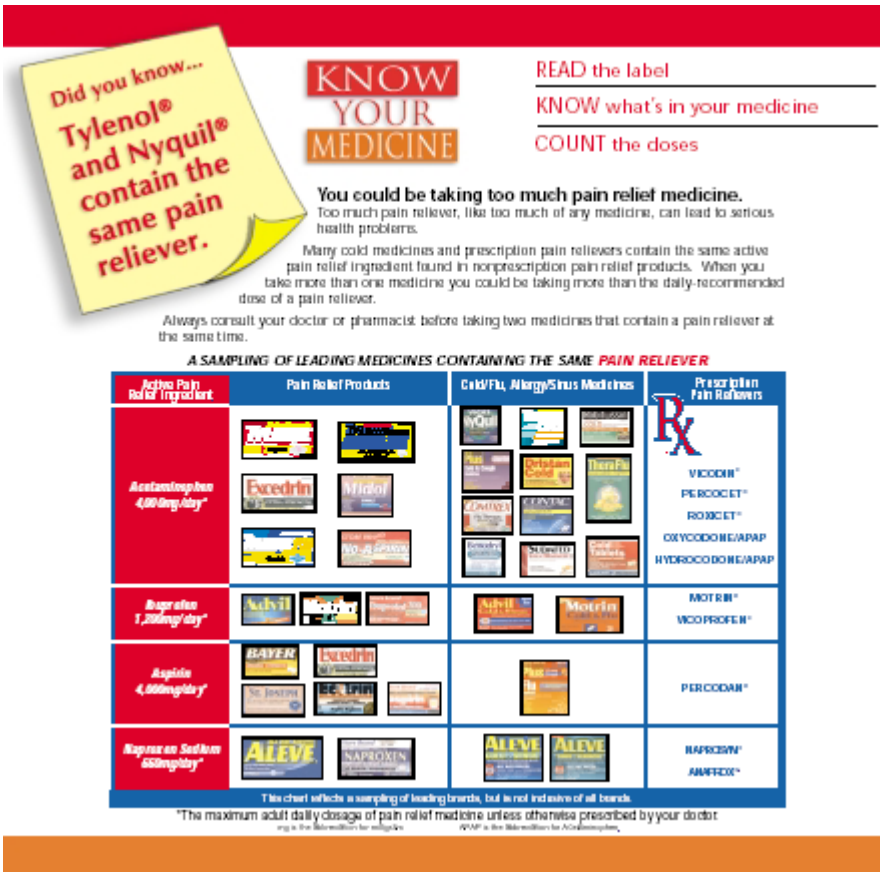
- Distribution of over 11 million "Know Your Medicine" consumer education brochures, in English and Spanish, in retail stores, by direct mail, at pharmacy counters, and doctors' offices through 2002.
- Retailer partnerships established to develop retailer-branded brochures that incorporate the "Know Your Medicine" message (eg, CVS, Target, Walgreens, and Walmart).
- Placement of a home page promotional module on McNeil brand web sites and a link to the NCPIE Be MedWise web site.
- A direct mail and e-mail correspondence with consumers in the McNeil database following requests for additional information.
- Use of doctors' offices to distribute additional tip cards, brochures, and sheets from patient education tear pads.
- Creation of print advertisements of pediatric dosing in English and Spanish in publications with strong parent readership.

- A campaign targeted directly to Hispanic consumers (with television, print, and radio ads).

An example of the educational content is seen in the following figure. It shows the emphasis upon warning against use of multiple products containing the same analgesic and helping consumers to identify where that might be a problem.

Figure 6-3. McNeil's Know Your Medicine Brochure (Front)

Figure 6-4. Know Your Medicine Brochure (Back)



6.3.2.2 Educational Interventions Targeting Healthcare Providers and Professional and Non-Profit Organizations

NCPIE's "Be MedWise" Campaign

In January 2002, NCPIE launched the nationwide "Be MedWise" program, a multi-media effort to increase public awareness of OTC product ingredients and their uses. The program was developed by NCPIE through an educational grant from McNeil. It was designed to attract support from other manufacturers as well. This effort has proven successful. On August 15, 2002, Proctor and Gamble announced its support with a $1 million educational grant toward the "Be MedWise" campaign. McNeil is optimistic that additional sponsors will participate.

The program includes television and print advertisements, and an Internet web site (www.bemedwise.org). Many of the materials have been developed in cooperation with the

FDA. For example, NCPIE has a television advertisement aimed at avoiding the use of more than one medication containing the same active ingredient. The ad has already reached 70% of the US population and has been seen over one billion times. It features a man, who, on the advice of his wife, reads the labels of the drugs he is taking and discovers that he is taking two drugs with the same active ingredient for the same indication.

The "Be MedWise" website has been featured on CNN. Key website communication points include:

- "Know What's in Your Medicine" - designed to encourage consumers to read medication labels to understand the active ingredient(s) in the OTC product they have purchased.
- "How to Read a Drug Label" - designed to encourage consumers to read medication labels and to help them understand the safety and use information present on the label.

Phase II of the campaign, launched on May 16, 2002, features an expanded consumer-friendly website, advertisement in two issues of TIME magazine, and an expanded media outreach.

Other Professional Organization Education Initiatives

McNeil initiatives include efforts to promote physicians', pharmacists', and other healthcare professionals' awareness of tools to reduce the occurrence of inappropriate OTC analgesic use. Working in cooperation with various professional organizations, McNeil has sponsored materials directed towards this objective.

For example, the American Association of Family Physicians (AAFP) has developed a monograph entitled "Appropriate Use of Common OTC Analgesics and Cough and Cold Medications" [Montauk 2002] and supporting patient education tools. This includes "Knowing What's in the Medicine You Take," a guide to using OTC pain relievers and prescription medicines. These materials were developed with an educational grant from McNeil. They were distributed to all 93,000 AAFP members and 30,000 other primary care physicians.

In an effort to improve pharmacist awareness, McNeil has sponsored a National Association of Chain Drug Stores (NACDS) memo containing extensive information on the importance of proper dosing to be included in the Chain Pharmacist Practice Memo. Building on a previously established partnership with the American Pharmaceutical Association (APhA), McNeil is developing several monographs for use in pharmacist

continuing education including, “The Pharmacist’s Role in Assuring OTC Medication Use,” Achieving Optimal Therapeutic Outcomes with Nonprescription Analgesics,” and “Health Communication in Culturally Diverse Patient Populations.” These monographs will be sent to over 55,000 pharmacists in the US.

6.3.3 Current Consumer OTC Analgesic Use Monitoring

McNeil is dedicated to evaluating the impact of its current labeling and education interventions described above on reported consumer behavior and awareness. To this end, McNeil has entered into an agreement with the Slone Epidemiology Center to expand their ongoing telephone survey of consumer behaviors regarding medications [Kaufman 2002].

Slone is adding questions to monitor changes in reported consumer behavior and to allow adjustments to OTC analgesic use-related consumer education and labeling initiatives (ie, to examine the impact of these initiatives on consumer behaviors). Data collection began in mid-June 2002. Consumers are asked about usage of any OTC analgesic product during the previous week. Respondents are asked about the dosages taken for each OTC analgesic used and sources they use to obtain information about these products. In addition, respondents are asked about their knowledge of product ingredient(s), the recommended labeled dose and knowledge of multiple-products with the same analgesic ingredient.

This periodic assessment of consumer behaviors will provide a tool to measure changes in consumer awareness and reported behaviors that arise in response to targeted messages from our consumer education programs, as well as from labeling revisions to OTC and prescription products that contain acetaminophen.

6.4 Conclusions

McNeil has reviewed survey and other data that provide insights for the interventions we have implemented. These interventions are designed to target the small group of consumers who may inadvertently exceed recommended doses of OTC analgesics. Excessive doses of an OTC analgesic may be taken inadvertently because an individual does not pay attention to the product label, does not understand the product label, or is not sufficiently concerned about the potential ramifications of exceeding the recommended dose [personal communication Carr 2002]. McNeil has initiated interventions that include pediatric labeling and dosing device modifications, and labeling revisions to OTC single and combination products as well as prescription acetaminophen-containing analgesics. Implemented McNeil initiatives include consumer and healthcare educational programs and an ongoing consumer OTC analgesic use monitoring survey.

7 ATTACHMENTS

Attachment 1: Academic Affiliations for each Member of the Expert Review Panel

Expert Review Panel

Member Names and Academic Affiliations

Gordon D. Benson, MD
Professor of Medicine, Associate Dean
Robert Wood Johnson Medical School
Camden, NJ

Martin Caravati, MD
Medical Director
Division of Emergency Medicine
University of Utah
Salt Lake City, UT

Richard C. Dart, MD, PhD
Director
Rocky Mountain Poison & Drug Center
Denver, CO

Raymond S. Koff, MD
Director of Clinical Hepatology Research
University of Massachusetts Memorial Medical Center
Worcester, MA

Victor J. Navarro, MD
Clinical Professor of Medicine
Thomas Jefferson University
Philadelphia, PA

Kent R. Olson, MD
Medical Director
Poison Control Center of San Francisco General Hospital
San Francisco, CA

Barry H. Rumack, MD
Clinical Professor of Pediatrics
Director Emeritus
Rocky Mountain Poison & Drug Center
Denver, CO

Donna Seger, MD
Assistant Professor of Emergency Medicine
Vanderbilt University Medical Center
Nashville, TN

K. V. Speeg, MD, PhD
Professor, Department of Medicine
University of Texas Health Science Center
San Antonio, TX

Attachment 2: Causality Data Form

Mfr. Report Number (see 9 on MedWatch) _____ Reviewer's Name_____

ACETAMINOPHEN HEPATOTOXICITY CAUSALITY DATA COLLECTION INSTRUMENT

1. Does case include adequate information for evaluation?

To be considered a case must include BOTH of the following:

- A history of acetaminophen ingestion or a serum level with acetaminophen present.
- Evidence of liver injury of any type

Should case be evaluated? Yes ____ No ____

If NO, STOP HERE!

2. Working Definition of Acetaminophen Causation

A case of acetaminophen induced hepatic injury may have occurred when evidence of liver injury is present in a patient with acetaminophen exposure in the absence of an equally or more likely alternative cause.

1. Is evidence of acetaminophen ingestion present?

Check all that apply:

- History of acetaminophen ingestion? Y N ?
- Positive serum acetaminophen level?

  What was first serum acetaminophen level reported? (mcg/ml or mg/L) Y N ?

  What was time of level post ingestion? Circle one:

  Admission, Not Reported, or ____ hrs post ingestion

2. Is evidence of liver injury present?

Check all that apply:

- AST or ALT greater than 500 IU/L at any time Y N ?
- Evidence of clinical signs of acute liver injury or failure Y N ?
- Statement of "liver failure" or similar comment (e.g. liver histopathology showing injury) is present Y N ?

3. Is there an equally or more likely alternative cause in the report?

Check all that apply:

- Infectious liver disease? Y N ?
- Inconsistent liver histopathology or presence of other anatomical liver conditions (e.g. Budd-Chiari syndrome)? Y N ?
- Potential confounding drug or drug interaction ? Y N ?
- Hypotension or shock or severe hypoxemia present during course? Y N ?
- Serum acetaminophen level that is inconsistent with reported history? Y N ?
- Other inconsistency of clinical course or plausible alternative cause of liver injury that questions relationship Y N ?
- Evidence of hypersensitivity reaction? Y N ?

Mfr. Report Number (see 9 on MedWatch) _____ Reviewer's Name_____

FINAL ASSESSMENT (Check one)

Evaluable Case:
Sufficient information is available → INSUFFICIENT
↓
Case is consistent with APAP toxicity → No → DEFINITELY NOT APAP
↓
Alternative diagnosis more likely → Yes → UNLIKELY
↓
(No more likely diagnosis)
↓
Still Absent "key" Information → Yes → POSSIBLE
↓
(Sufficient "key" data)
↓
More than 50 % clinical probability → Yes → PROBABLE
↓
Nearly 100% clinical probability → Yes → DEFINITE

Acetaminophen definitely caused liver injury ____
(Nearly 100% certainty that APAP was the cause of liver injury)

Acetaminophen probably caused liver injury ____
(Greater than 50% clinical certainty that APAP was the cause of liver injury)

Acetaminophen possibly caused liver injury ____
(Case is consistent with APAP as cause, but other confounders or alternative explanations are present; less than 50% clinical certainly that APAP was cause of liver injury)

Acetaminophen was unlikely the cause of liver injury ____
(Alternative explanation seems clinically more likely than APAP)

Acetaminophen was not cause of liver injury ____
(Nearly 100% certainty that APAP was NOT the cause of liver injury)

Data available are insufficient to determine causality ____
(Even if the case may be consistent with APAP cause, crucial data are simply not present.)

DOSE ASSESSMENT
What is the body burden of acetaminophen (see table) ____

If a serum acetaminophen level is available (timed or untimed), is the body burden consistent with the reported dose?

1. **Yes**
2. **No. Please Explain _____**
3. **Can't evaluate**

8 REFERENCE LIST

The reference materials are listed in alphabetical order by section.

Section 2: Efficacy of Acetaminophen in the Treatment of Pain

Agency for Healthcare Research and Quality. Management of Cancer Pain. [Summary] Rockville, MD: AHRQ, January 2001; Evidence Report/Technology Assessment: Number 35. AHRQ Publication No. 01-E033.

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

Amadio P Jr, Cummings DM: Evaluation of acetaminophen in the management of osteoarthritis of the knee. Curr Ther Res 1983 Jul;34(1):59-66.

Amadio P Jr. Peripherally acting analgesics. Am J Med 1984 Sep 10; 17-26.

Ameer B, Divoll M, Abernethy DR, et al. Absolute and relative bioavailability of oral acetaminophen preparations. J Pharm Sci 1983 Aug;72(8):955-958.

American Academy of Orthopaedic Surgeons/American Association of Neurological Surgeons/American College of Physical Medicine and Rehabilitation/American College of Rheumatology. Clinical guideline on hip pain 1996.

American Academy of Pediatrics/Canadian Paediatric Society. Prevention and management of pain and stress in the neonate. 2000 Feb.

American College of Radiology (ACR) Expert Panel on Neurologic Imaging. ACR Appropriateness Criteria™: Acute low back pain—Radiculopathy. Reston, VA: ACR, 1999.

American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000 Sep;43(9):1905-1915.

American Geriatrics Society (AGS) Panel on Chronic Pain in Older Persons. The management of chronic pain in older persons. J Am Geriatr Soc 1998 May;46(5):635-651.

American Geriatrics Society (AGS) Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc 2002 Jun:50(S6) (supplement).

American Medical Directors Association (AMDA). Chronic Pain Management in the Long-Term Care Setting. Columbia MD: AMDA, 1999.

American Pain Society (APS). Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease. Glenview, IL: APS, 1999.

American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Practice Guidelines for Chronic Pain Management. Anesthesiology 1997 Apr;86(4):995-1004.

Bedjaoui A, Demotes-Mainard F, Raynal F, et al. Influence de l'âge et du sexe sur la pharmacocinétique du paracétamol [Influence of age and sex on the pharmacokinetics of paracetamol]. Thérapie 1984;39:353-359.

BenDebba M, Torgerson WS, Long DM. Personality traits, pain duration and severity, functional impairment, and psychological distress in patients with persistent low back pain. Pain 1997;72:115-125.

Borin MT, Ayres JW. Single dose bioavailability of acetaminophen folllowing oral administration. Int J Pharm 1989;54:199-209.

Bradley JD, Brandt KD, Katz BP, et al: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991 Jul 11;325(2):87-91.

Carr AJ. Beyond disability: Measuring the social and personal consequences of osteoarthritis. Osteoarthritis Cartilage 1999;7(2):230-238.

Carr D, Chao S, Polomano R, et al. Restricting dosage or availability of OTC analgesics: A model for analysis. 2002 (unpublished).

Casten RJ, Parmelee PA, Kleban MH, et al. The relationships among anxiety, depression, and pain in a geriatric institutionalized sample. Pain 1995;61:271-276.

Christophersen AB, Levin D, Hoegberg LC, et al. Activated charcoal alone or after gastric lavage: A simulated large paracetamol intoxication. Br J Clin Pharmacol 2002 Mar;53(3):312-317.

Cousins M. Acute and postoperative pain. In: Wall PD, Melzack R, eds. Textbook of Pain, 3rd ed. New York: Churchill Livingstone, 1994:357-385.

Desbiens NA, Mueller-Rizner N, Connors AF Jr, et al. HELP Investigators: Pain in the oldest-old during hospitalization and up to one year later. J Am Geriatr Soc 1997 Oct;45(10):1167-1172.

Divoll M, Abernathy DR, Ameer B, et al. Acetaminophen kinetics in the elderly. Clin Pharmacol Ther 1982; 31:151-156.

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

Divoll M, Greenblatt DJ, Ameer B, et al. Effect of food on acetaminophen absorption in young and elderly subjects. J Clin Pharmacol 1982 Nov/Dec;22:571-576.

Douglas, DR, Sholar, JB, Smilkstein MJ. A pharmacokinetic comparison of acetaminophen products (Tylenol® Extended Relief vs Regular Tylenol®). Acad Emerg Med 1996 Aug;3:740-744.

Dworkin RH. Which individuals with acute pain are most likely to develop a chronic pain syndrome? Pain Forum 1997;6:127-36.

Ferrell BR, Griffith H. Cost issues related to pain management: Report from the cancer pain panel of the agency for health care policy and research. J Pain Symptom Manage 1994 May;9(4):221-234.

Foley KM. Pain relief into practice: Rhetoric without reform. J Clin Oncol 1995 Sep;13(9):2149-2151 (editorial).

Furdon SA, Eastman M, Benjamin K, et al. Outcome measures after standardized pain management strategies in postoperative patients in the neonatal intensive care unit. J Perinat Neonatal Nurs 1998 Jun;12(1):58-69.

Geba GP, Weaver AL, Polis AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: A randomized trial. JAMA 2002 Jan 2;287(1):64-71.

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

Gottschalk A, Smith DS, Jobes DR, et al. Preemptive epidural analgesia and recovery from radical prostatectomy: A randomized controlled trial. JAMA 1998 Apr 8;279(14):1076-1082.

Grant M, Ferrell BR, Rivera LM, et al. Unscheduled readmissions for uncontrolled symptoms: A health care challenge for nurses. Nurs Clin North Am 1995 Dec;30(4):673-682.

Grattan T, Hickman R, Darby-Dowman A, et al. A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate. Eur J Pharm Biopharm 2000;49:225-229

Green R, Grierson R, Sitar DS, et al. How long after drug ingestion is activated charcoal still effective? Clinical Toxicology 2001;31(6):601-605

Gureje O, Von Korff M, Simon GE, et al. Persistent pain and well-being: A World Health Organization study in primary care. JAMA 1998 Jul;280(2):147-151.

Gustafsson I, Nystrom E, Quiding H. Effects of preoperative paracetamol on pain after oral surgery. Eur J Clin Pharmacol 1983;24:63-65.

Haack DG. A phase IV collaborative multi-clinic, double-blind study to compare efficacy of and side effects profile of acetaminophen and ibuprofen in the treatment of pain secondary to osteoarthritis. Stat Rpt 72. Protocol 3-277, Unpublished Report 192, September 1986.

Heim HM, Oei TP. Comparison of prostate cancer patients with and without pain. Pain 1993;53:159-162.

Hindmarsh KW, Mayers DJ, Wallace SM, et al. Increased serum sulfate concentrations in man due to environmental factors: Effects on acetaminophen metabolism. Vet Hum Toxicol 1991 Oct;33(5):441-445.

Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Arthritis Rheum 1995;38:1535-1546.

Hopkinson JH, Smith MT, Bare WW, et al. Acetaminophen (500 mg) versus acetaminophen (325 mg) for the relief of pain in episiotomy patients. Curr Ther Res 1974 Mar;16(3):194-200.

Hutcheson SJ, Mason WD. Pharmacodynamic modeling of the analgesic properties of specific non-opioid analgesics using the dental pain model. 1993 (abstract).

Joint Commission on Accreditation of Healthcare Organizations Pain Standards, 2001.

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

Katz J. Pre-emptive analgesia: Evidence, current status and future directions. Eur J Anaesthesiol 1995;12 (Suppl. 10):8-13.

Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996;12(1):50-55.

Kiersch TA, Halladay SC, Hormel PC. A single-dose, double-blind comparison of naproxen sodium, acetaminophen, and placebo in postoperative dental pain. Clin Ther 1994;16(3):394-404.

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

Lee SH, Kim SI, Yoo WH, et al. The comparison of the efficacy and gastrointestinal side effects of Tylenol-ER (extended relief) and naproxen in patients with osteoarthritis of the knee: Multicenter clinical trial. J Korean Rheum Arthritis Soc 1998 Nov;5(2):211-220.

Liebeskind JC. Pain *can* kill. Pain 1991;44:3-4 (guest editorial).

Linton SJ. Overlooked and undertreated? The role of acute pain intensity in the development of chronic low back pain problems. Pain Forum 1997;6:145-7.

Liu S, Carpenter RL, Neal JM. Epidural Anesthesia and Analgesia: Their role in postoperative outcome. Anesthesiology 1995 Jun;82(6):1474-1506 (review).

Louis Harris & Associates. Pain and Absenteeism in the Workplace. Business and Health 1996. Available at http://208.153.7.109/resources/reports/related_news_0301.html (accessed 8/29/02).

McCaffrey M, Pasero BR. Pain: Clinical Manual. 1999. St Louis: Mosby.

McNeil Laboratories. NDA 170-53: Amendment No 1: Clinical Study Data 1972 December 19.

McQuay HJ, Poppleton P, Carroll D, et al. Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther 1986;39(1):89-93.

McQuay HJ, Edwards JF, Moore RA. Evaluating analgesia: The challenges. Am J Ther 2002;9(3):179-187.

Mehlisch DR, Jasper RD, Brown P, et al. Comparative study of ibuprofen lysine and acetaminophen in patients with postoperative dental pain. Clin Ther 1995;17(5):852-860.

Miaskowski C, Kragness L, Dibble S, et al. Differences in mood states, health status, and caregiver strain between family caregivers of oncology outpatients with and without cancer-related pain. J Pain Symptom Manage 1997;13:138-147.

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

Mitchell MC, Hanew T, Meredith CG, et al. Effects of oral contraceptive steroids on acetaminophen metabolism and elimination. Clin Pharmacol Ther 1983 Jul;34(1):48-53.

Nick JB. A single-dose, double-blind, placebo-controlled study of the relative efficacy and safety of acetaminophen at doses of 500mg and 1000mg in postoperative dental pain. McNeil Consumer & Specialty Pharmaceuticals Protocol 02-156. Data on file. 2002

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

Nystrom E, Gustafsson I, Quiding H. The pain intensity at analgesic intake and the efficacy of diflunisal in single doses and effervescent acetaminophen in single and repeated doses. Pharmacotherapy 1988;8(3):201-209.

Page GG. The medical necessity of adequate pain management. Pain Forum 1996;5:227-31.

Parier JL, Pichard O, Bonhomme L, et al. Bioavailability of paracetamol according to pharmaceutical form. J Pharm Belg 1988;43(3):287-291.

Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2000;59:936-944.

Pigeon JG, Nick JB. A comparative study using a single dose of acetaminophen, acetaminophen/pseudoephedrine, pseudoephedrine alone, and placebo in dental pain. CSR 163. Protocol 91-123, Unpublished Report 289, November 1992.

Quiding H, Oikarinen V, Sane J, et al. Analgesic efficacy after single and repeated doses of codeine and acetaminophen. J Clin Pharmacol 1984;24(1):27-34.

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

Riley LA. Pain management facilitates early postoperative recovery. Prog Cardiovasc Nurs 1996;11(1):47-48.

RW Johnson Pharmaceutical Research Institute Clinical Study Report 1999a: Evaluation of the efficacy and safety of tramadol/APAP in oral surgical pain. Protocol TRAMAP-ANAG. Unpublished report 3996. 1999 July.

RW Johnson Pharmaceutical Research Institute Clinical Study Report 1999b: Evaluation of the efficacy and safety of tramadol/APAP in oral surgical pain. Protocol TRAMAP-ANAG. Unpublished report 3997. 1999 July.

RW Johnson Pharmaceutical Research Institute Clinical Study Report 1999c: Evaluation of the efficacy and safety of tramadol/APAP in oral surgical pain. Protocol TRAMAP-ANAG. Unpublished report 3999. 1999 July.

Sajahawalla CG, Ayres JW. Multiple-dose acetaminophen pharmacokinetics. J Pharm Sci 1991 Sept;80(9):855-860.

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

Seymour RA, Kelly PJ, Hawkesford JE. The efficacy of ketoprofen and paracetamol (acetaminophen) in postoperative pain after third molar surgery. Brit J Clin Pharmacol 1996;41(6):581-585.

Sheehan J, McKay J, Ryan M, et al. What cost chronic pain? Ir Med J 1996 Nov/Dec;89(6):218-219.

Silberstein EB, Taylor AT for the Society of Nuclear Medicine, Procedure Guideline for Bone Pain Treatment 2.0, Reston, VA: 1999 Feb. available at www.snm.org.

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

Skjelbred P, Løkken P, Skoglund LA. Postoperative administration of acetaminophen to reduce swelling and other inflammatory events. Curr Thera Res 1984 Mar;35(3):377-385.

Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. Pharmacotherapy 1991;11(5):364-369.

Snelling J. The effect of chronic pain on the family unit. J Adv Nurs 1994;19:543-551.

Sorge J. The lesson from cancer pain. Eur J Pain 2000:A (suppl A);3-7

Stork, CM, Rees S, Howland MA et al. Pharmacokinetics of extended relief versus regular release Tylenol in simulated human overdose. Clin Toxicol 1996;34(2):157-162.

Tasmuth T, von Smitten K, Hietanen P, et al. Pain and other symptoms after different treatment modalities of breast cancer. Ann Oncol 1995;6:453-459.

Veterans Health Administration/Department of Defense (VHA/DOD). VHA/DOD clinical practice guideline for the management of low back pain or sciatica in the primary care setting. Washington, D.C.: VHA Headquarters, May 1999; Contract number: V101(93)P-1633.

Wade AG, Ward PJ. A double-blind comparison of meptazinol versus paracetamol and placebo in acute and chronic painful conditions presenting to the general practitioner. Curr Med Res Opin 1982;8(3):191-196.

Washington State Department of Labor and Industries/ Washington State Medical Association. Fibromyalgia. 1999.

World Health Organization. Cancer pain relief: A guide to opioid availability. 2nd ed. Geneva: World Health Organization, 1996.

World Health Organization Expert Committee on Cancer Pain Relief and Active Supportive Care. Cancer Pain Relief and Palliative Care. Geneva: World Health Organization, 1990; WHO Technical Report Series 804.

Yiamouyiannis CA, Harris A, Sanders RA. Paracetamol Pharmacokinetics are independent of caloric intake and physical activity. Drug Invest 1994; 8(6):361-368.

Yuan CS, Karrison T, Wu JA, et al. Dose-related effects of oral acetaminophen on cold-induced pain: A double-blind, randomized, placebo-controlled trial. Clin Pharmacol Ther 1998;63(3):379-383

Zoppi M, Perett G, Boccard E. Paracetamol and arthritis: Placebo-controlled study of the analgesic efficacy of an effervescent formulation of 500 mg paracetamol in arthritis of the knee or hip. Eur J Pain 1995;16(1-2):42-48.

Section 3: Acetaminophen Pharmacology and Toxicology

Ameer B, Divoll M, Abernethy DR, et al. Absolute and relative bioavailability of oral acetaminophen preparations. J Pharm Sci 1983 Aug;72(8):955-958

Autret E, Dutertre J-P, Bretau M, et al. Pharmacokinetics of paracetamol in the neonate and infant after administration of propacetamol chlorhydrate. Dev Pharmacol Ther 1993;20:129-134.

Bannwarth B, Netter P, Lapicque F, et al. Plasma and cerebrospinal fluid concentrations of paracetamol after a single intravenous dose of propacetamol. Br J Clin Pharmacol 1992;34:79-81.

Bedjaoui A, Demotes-Mainard F, Raynal F, et al. Influence de l'âge et du sexe sur la pharmacocinétique du paracétamol [Influence of age and sex on the pharmacokinetics of paracetamol]. Thérapie 1984;39:353-359.

Benson GD. Acetaminophen in chronic liver disease. Clin Pharmacol Ther 1983 Jan;33(1):95-101.

Blackledge HM, O'Farrell J, Minton NA, et al. The effect of therapeutic doses of paracetamol on sulphur metabolism in man. Hum Exp Toxicol 1991 May; 10(3): 159-65.

Borin MT, Ayres JW. Single dose bioavailability of acetaminophen folllowing oral administration. Int J Pharm 1989;54:199-209.

Botting RM. Mechanism of action of acetaminophen: Is there a cyclooxygenase 3? Clin Infect Dis 2000;31(Supp 5):S202-S210.

Boutaud O, Aronoff DM, Richardson JH, et al. Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandin H_2 synthases. PNAS 2002;99(10):7130-7135.

Briant RH, Dorrington RE, Cleal J, et al. The rate of acetaminophen metabolism in the elderly and the young. J Am Geriatr Soc 1976 Aug; 24(6):359-361.

Brown RD, Wilson JT, Kearns GL, et al. Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. J Clin Pharmacol 1992 Mar;32(3):231-241.

Christophersen AB, Levin D, Hoegberg LC, et al. Activated charcoal alone or after gastric lavage: A simulated large paracetamol intoxication. Br J Clin Pharmacol 2002 Mar;53(3):312-317.

Court MH, Duan SX, Von Moltke LL, et al. Interindividual variability in acetaminophen glucuronidation by human liver microsomes: Identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. J Pharmacol Exp Ther 2001;299(3):998-1006.

Davis M, Simmons CJ, Harrison NG, et al. Paracetamol overdose in man: Relationship between pattern of urinary metabolites and severity of liver damage. Quarterly Journal of Medicine New Series XLV 1976 Apr;178:181-191.

Desmeules J, Piguet V, Dayer P. Nociceptive flexion reflex (R-III) as a tool to assess the antinociceptive effect of central analgesics. Clin Pharm Ther 1995 Feb;57(3):139.

Divoll M, Abernathy DR, Ameer B, et al. Acetaminophen kinetics in the elderly. Clin Pharmacol Ther 1982a; 31:151-156.

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

Divoll M, Greenblatt DJ, Ameer B, et al. Effect of food on acetaminophen absorption in young and elderly subjects. J Clin Pharmacol 1982c Nov/Dec;22:571-576.

Douglas, DR, Sholar, JB, Smilkstein MJ. A pharmacokinetic comparison of acetaminophen products (Tylenol Extended Relief vs Regular Tylenol). Acad Emerg Med 1996 Aug;3:740-744.

Ellmers SE, Parker, LRC, Notarianni LJ, et al. Excretion of paracetamol in fit and frail elderly people. Br J Clin Pharmacol 1990 May;31(5):596P-597P (abstract).

Forrest JA, Adriaenssens P, Finlayson ND, Prescott LF. Paracetamol metabolism in chronic liver disease. Eur J Clin Pharmacol 1979;15:427-431.

Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet 1982;7:93-107.

Grattan T, Hickman R, Darby-Dowman A, et al. A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing

paracetamol in combination with sodium bicarbonate or calcium carbonate. Eur J Pharm Biopharm 2000;49:225-229.

Green R, Grierson R, Sitar DS, et al. How long after drug ingestion is activated charcoal still effective? Clinical Toxicology 2001;31(6):601-605

Hassig SR, Linscheer WG, Murthy UK, et al. Effects of PEG-electrolyte (colyte) lavage on serum acetaminophen concentrations: A model for treatment of acetaminophen overdose. Dig Dis Sci 1993 Aug;38(8):1395-1401.

Hendrix-Treacy, Wallace SM, Hindmarsh KW, et al. The effect of acetaminophen administration on its disposition and body stores of sulphate. Eur J Clin Pharmacol 1986;30:273-278.

Hindmarsh KW, Mayers DJ, Wallace SM, et al. Increased serum sulfate concentrations in man due to environmental factors: Effects on acetaminophen metabolism. Vet Hum Toxicol 1991 Oct;33(5):441-445.

Hopkins CS, Underhill S, Booker PD. Pharmacokinetics of paracetamol after cardiac surgery. Arch Dis Child 1990;65:971-976.

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

Kelley MT, Walson PD, Edge JH, et al. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. Clin Pharmacol Ther 1992 Aug;52(2):181-189.

Kobrinsky NL, Hartfield D, Horner H, et al. Treatment of advanced malignancies with high-dose acetaminophen and *N*-acetylcysteine rescue. Cancer Invest 1996;14(3):202-210.

Koch-Weser J. Medical Intelligence: Drug Therapy. N Engl J Med 1976 Dec 2;295(23):1297-1300.

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

Lauterberg BH, Mitchell JR. Therapeutic doses of acetaminophen stimulate the turnover of cysteine and glutathione in man. J Hepat 1987;4:206-211

Lee HS, Ti TY, Koh, YK, et al. Paracetamol elimination in Chinese and Indians in Singapore. Eur J Clin Pharmacol 1992;43:81-84.

Levy G, Khanna NN, Soda DM, et al. Pharmacokinetics of acetaminophen in the human neonate: Formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and D-glucaric acid excretion. Pediatrics 1975 June;55(6):818-825.

Levy G. Comparative Pharmacokinetics of aspirin and acetaminophen. Arch Intern Med 1981 Feb 23;141:279.

Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000 Mar;67(3):275-282.

McNeil Consumer Healthcare Bioequivalence Study Report for Protocol 89-956 (BS-92): A comparison of sustained-release AC caplet formulation and a conventional tablet formulation under multiple dose conditions. Fort Washington, PA: McNeil Consumer Healthcare, July 1990. Submitted to NDA 19-872 Amendment No. 4 on October 29, 1992.

McNeil Consumer Healthcare Bioequivalence Study Report for Protocol 98-054: Bioequivalence determination of extra strength Tylenol gelcaps and caplets with extra strength Tylenol tablets. Fort Washington PA: McNeil Consumer Healthcare, May 2001.

McNeil Consumer and Specialty Pharmaceuticals Pharmacokinetic Study for Protocol 02-161: Tolerability and multiple-dose pharmacokinetics of acetaminophen (paracetamol) at and above the currently recommended maximum daily dose. Fort Washington, PA, July 2002 . Data on file.

Milligan TP, Morris HC, Hammond PM, et al. Studies on paracetamol binding to serum proteins. Ann Clin Biochem 1994; 31:492-496

Milton AS. Modern views on the pathogenesis of fever and the mode of action on antipyretic drugs. J Pharm Pharmacol 1976;28:393-399.

Miners JO, Atwood J, Birkett DJ. Influence of sex and oral contraceptive steroids on paracetamol metabolism. Br J Clin Pharmacol 1983;16:503-509

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

Miners JO, Osborne NJ, Tonkin AL, et al. Perturbation of paracetamol urinary metabolic ratios by urine flow rate. Br J Clin Pharmacol 1992;34:359-362.

Mitchell JB, Jollow DJ, Potter WZ. Acetaminophen-induced hepatic necrosis: I. Role of drug metabolism. J Pharmacol Exp Therapeut 1973 Oct;187:185-194.

Mitchell JR, Thorgeirsson SS, Potter WZ, et al. Acetaminophen-induced injury: Protective role of glutathione in man and rationale for therapy. Clin Pharmacol Ther 1974;16:676-684.

Mitchell MC, Hanew T, Meredith CG, et al. Effects of oral contraceptive steroids on acetaminophen metabolism and elimination. Clin Pharmacol Ther 1983 Jul;34(1):48-53.

Nahata MC, Powell DA, Durell DE. Acetaminophen (APAP) kinetics in infants and children after single and repeated doses. Eur J Clin Pharmacol 1984;27:57-59.

Ouellet M, Percival MD. Mechanisms of acetaminophen inhibiton of cyclooxygenase isoforms. Archives of Biochemistry and Biophysics 2001;3987(2):273-280.

Parier JL, Pichard O, Bonhomme L, et al. Bioavailability of paracetamol according to pharmaceutical form. J Pharm Belg 1988;43(3):287-291.

Piguet V, Desmeules J, Dayer P. Lack of acetaminophen ceiling effect on R-III nociceptive flexion reflex. Eur J Clin Pharmacol 1998 Jan;53(5):321-324.

Piletta P, Porchet HC, Dayer P. Pharmacodynamics and drug action: Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 1991 Apr;49(4):350-354.

Prescott LF. Drug conjugation in clinical toxiology. Biochem Soc Trans 1984 Feb;12(1):96-99.

Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmacol 1980;10:291S-298S.

Prescott LF. Paracetamol overdosage: Pharmacological considerations and clinical management. Drugs 1983 Mar 25(3):290-314.

Prescott LF, Wright N, Roscoe P, et al. Plasma-paracetamol half life and hepatic necrosis in patients with paracetamol overdosage. Lancet 1971 Mar 13;519-522.

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

Rømsing J, Ostergaard D, Senderovitz T, et al. Pharmacokinetics of oral diclofenac and acetaminophen in children after surgery. Paediatr Anaesth 2001 Mar;11(2):205-213.

Rose SR, Gorman RL, Oderda GM, et al. Simulated acetaminophen overdose: Pharmacokinetics and effectiveness of activated charcoal. Ann Emerg Med 1991; 20: 1064-1068.

Rumack BH, Matthews H. Acetaminophen poisoning and toxicity. Pediatrics1975 Jun; 55(6):871-6.

Rumack BH. Acetaminophen hepatotoxicity: The first 35 years. Clinical Toxicology 2002;40(1):3-20.

Sajahawalla CG, Ayres JW. Multiple-dose acetaminophen pharmacokinetics. J Pharm Sci 1991 Sept;80(9):855-860.

Shayiq RM, Roberts DW, Rothstein K, et al. Repeat exposure to incremental doses of acetaminophen provides protection against acetaminophen-induced lethality in Mice: An

explanation for high acetaminophen dosage in humans without hepatic injury. Hepatology 1999 Feb;29(2):451-463.

Simmons DL, Botting RM, Robertson PM. Induction of an acetaminophen-sensitive cyclooxygenase with reduced sensitivity to nonsteroid antiinflammatory drugs. Proc Natl Acad Sci USA 1999 Mar;96:3275-3280.

Simmons DL. Wagner D, Westover K. Nonsteroidal anti-inflammatory drugs, acetaminophen, cyclooxygenase2, and fever. Clin Infect Dis 2000;31(Suppl 5):S211-S218.

Slattery JT, Levy G. Acetaminophen kinetics in acutely poisoned patients. Clin Pharmacol Ther 1979 Feb;25(2):184-95.

Slattery JT, McRorie TI, Reynolds R, et al. Lack of effect of cimetidine on acetaminophen disposition in humans. Clin Pharmacol Ther 1989 Nov;46(5):591-597.

Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). N Engl J Med 1988 Dec 15;319(24):1557-62.

Stork, CM, Rees S, Howland MA et al. Pharmacokinetics of extended relief versus regular release Tylenol in simulated human overdose. Clin Toxicol 1996;34(2):157-162.

Triggs EJ, Nation RL, Long A, et al. Pharmacokinetics in the Elderly. Eur J Clin Pharmacol 1975;8:55-62.

Vance MV, Selden BS, Clark RF. Optimal patient position for transport and initial management of toxic ingestions. Ann Emerg Med 1992 Mar;21(3):243-246.

Walson PD, Galletta G, Braden NJ, et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 1989 Jul;46(1):9-17.

Wessels JC, Koeleman HA, Boneschans B, et al. The influence of different types of breakfast on the absorption of paracetamol among members of an ethnic group. Int J Clin Pharm Ther Tox 1992;30(6):208-213.

Willer, J C. Comparative study of perceived pain and nociceptive flexion reflex in man. Pain 1977;3:69-80.

Willer, J.C. Nociceptive flexion reflexes as a tool for pain research in man. In: Desmedt JE, Ed. Advances in neurology: Motor control mechanisms in health and disease. New York: Raven Press, 1983;809-827.

Wynne HA, Cope LH, Herd B, et al. The association of age and frailty with paracetamol conjugation in man. Age Ageing 1990 Nov;19(6):419-424.

Yiamouyiannis CA, Harris A, Sanders RA. Paracetamol Pharmacokinetics are independent of caloric intake and physical activity. Drug Invest 1994; 8(6):361-368.

Section 4: Assessment of Acetaminophen Safety

AAPCC. Toxic Exposure Surveillance System (TESS): TESS exposures treated with NAC-PO, 1997: Medical outcomes by age (adults lumped). 2001 September 27.

Abernethy DR, Divoll M, Greenblatt DJ, et al. Obesity, sex and acetaminophen disposition. Clin Pharmacol Ther June 1982;31(6):783-790.

Al-Obaidy SS, McKiernan PJ, Li Wan Po A, et al. Metabolism of paracetamol in children with chronic liver disease. Eur J Clin Pharmacol 1996;50:69-76.

Altomare E, Leo MA, Sato C, et al. Interaction of ethanol with acetaminophen metabolism in the baboon. Biochem Pharmacol 1984;33(14):2207-2212.

Amadio P Jr, Cummings DM: Evaluation of acetaminophen in the management of osteoarthritis of the knee. Curr Ther Res 1983 Jul;34(1):59-66.

Anderson GD: A mechanistic approach to antiepileptic drug interactions. Ann Pharmacother 1998 May;32:554-563.

Andreasen PB, Hutters L: Paracetamol (acetaminophen) clearance in patients with cirrhosis of the liver. Acta Med Scand 1979; Suppl 624:99-105.

Banda PW, Quart BD. The effect of mild alcohol consumption in the metabolism of acetaminophen in man. Res Commun Chem Pathol Pharmacol 1982 Oct;38(1):57-70.

Bannwarth B, Pehourcq F, Lagrange F, et al. Single and multiple dose pharmacokinetics of acetaminophen (paracetamol) in polymedicated very old patients with rheumatic pain. J Rheumatol 2001;28:182-184.

Bedjaoui A, Demotes-Mainard F, Raynal F, et al. Influence de l'âge et du sexe sur la pharmacocinétique du paracétamol [Influence of age and sex on the pharmacokinetics of paracetamol]. Thérapie 1984;39:353-359.

Benson GD. Acetaminophen in chronic liver disease. Clin Pharmacol Ther 1983 Jan;33(1):95-101.

Blot WJ, McLaughlin JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. J Epidemiol Biostat 2000;5(2):137-142.

Bock KW, Forster A, Gscgaidmeier H, et al. Paracetamol glucuronidation by recombinant rat and human phenol UDP-glucuronosyltransferases. Biochem Pharmacol 1993;45(9):1809-1814.

Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucurononsyltransferase 1 in Gilbert's Syndrome. N Engl J Med 1995;333(18):1171-1175.

Bradley JD, Brandt KD, Katz BP, et al: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991 Jul 11;325(2):87-91.

Bray GP, Harrison PM, O'Grady JG, et al. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. Hum Exp Toxicol 1992;11:265-270.

Briant RH, Dorrington RE, Cleal J, et al. The rate of acetaminophen metabolism in the elderly and the young. J Am Geriatr Soc 1976 Aug; 24(6):359-361.

Broughan TA, Soloway RD. Acetaminophen hepatoxcity. Dig Dis Sci 2000 Aug;45(8):1553-1558.

Careddu P, Mereu T, Apollonio T. Studies on glucuroconjugation in infectious hepatitis: Half-life of NAPA as a test of liver function. Minerva Pediatr 1961;13:1619 (translation).

Chan MTV, et al. Single-dose pharmacokinetics of paracetamol and its conjugates in Chinese non-insulin-dependent diabetic patients with renal impairment. Eur J Clin Pharmacol 1997;52:285-288.

Chang TK, Yu L, Maurel P, et al. Enhanced cyclophosphamide and ifosfamide activation in primary human hepatocyte cultures : Response to cytochrome P-450 inducers and autoinduction by oxazaphosphorines. Cancer Res 1997 May;57:1946-1954.

Chien JY, Peter RM, Nolan CM, et al. Influence of polymorphic N-acetyltransferase phenotype on the inhibition and induction of acetaminophen bioactivation with long-term isoniazid. Clin Pharmacol Ther 1997;61:24-34.

Choffray DU, Crielaard JM, Albert A, et al. Comparative study of high bioavailability glaphenine and paracetamol in cervical and lumbar arthrosis. Clin Rheumatol 1987;6(4):518-525.

Court MH, Duan SX, Von Moltke LL, et al. Interindividual variability in acetaminophen glucuronidation by human liver microsomes: Identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. J Pharmacol Exp Ther 2001;299(3):998-1006.

Critchley JA, Cregeen RJ, Balali-Mood M, et al. Paracetamol metabolism in heavy drinkers. Br J Clin Pharmacol 1982;13:276P-277P.

Critchley JA, Dyson EH, Scott AW, et al. Is there a place for cimetidine or ethanol in the treatment of paracetamol poisoning? Lancet 1983 Jun;1:1375-1376.

Dargan PI, Wallace CI, Jones AL. An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. Emerg Med J 2002;19:206-209.

Dargere S, Collet T, Crampon D, et al. Lack of toxicity of acetaminophen in patients with chronic hepatitis C: A randomized controlled trial. Gastroenterology 2000; 118 (4,Suppl.2);A947.

Dart RC, Kuffner EK, Rumack BH. Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: A systematic review. Am J Therap. 2000;7:123-134.

De Morais SMF, Uetrecht JP, Wells PG. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's Syndrome. Gastroenterology 1992 February;102(2):577-586.

Diaz D, Fabre I, Daujay M, et al. Liver, pancreas, and biliary tract: Omeprazole in an aryl hydrocarbon-like inducer of human hepatic cytochrome P450. Gastroenterology 1990 Sep;99(3):737-747.

Divoll M, Abernathy DR, Ameer B, et al. Acetaminophen kinetics in the elderly. Clin Pharmacol Ther 1982a; 31:151-156.

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

Divoll M, Greenblatt DJ, Ameer B, et al. Effect of food on acetaminophen absorption in young and elderly subjects. J Clin Pharmacol 1982c Nov/Dec;22:571-576.

Edwards OM, Edwards P, Huskisson RT, et al. Paracetamol and renal damage. Br Med J 1971 Apr 10;2:87-89.

Ellmers SE, Parker LRC, Notarianni LJ, et al. Excretion of paracetamol in fit and frail elderly people. Proceedings of the BPS 1990:596p-597p.

Epstein MM, Nelson SD, Slattery JT, et al. Inhibition of the metabolism of paracetamol by isoniazid. Br J Clin Pharmacol 1991;31:139-142.

Erturk H, Celiker R, Aydin M, et al. Comparison of efficacy of tolerability of acemetacin and acetaminophen in the treatment of knee osteoarthritis. J Rheumatol Med Rehab 1998;9(3):157-161 (translation).

Esteban A, Pérez-Mateo M. Heterogeneity of paracetamol metabolism in Gilbert's syndrome. Eur J Drug Metab Pharmacokinet 1990;24(1):9-13.

Faich, GA. Adverse drug reaction monitoring. N Engl J Med 1986 Jun 12;314(24):1589-1592.

Food and Drug Administration. Drug Induced Liver Toxicity. 2001. Available at http://www.fda.gov/cder/livertox/default.html (accessed 8/29/02).

Forrest JA, Adriaenssens P, Finlayson ND, Prescott LF. Paracetamol metabolism in chronic liver disease. Eur J Clin Pharmacol 1979;15:427-431.

Fuhr U. Induction of drug metabolising enzymes: Pharmacokinetic and toxicological consequences in humans. Clin Pharmacokinet 2000 Jun;38(6):493-504.

Geba GP, Weaver AL, Polis AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: A randomized trial. JAMA 2002 Jan 2;287(1):64-71.

Goldman SA. Limitations and strengths of spontaneous reports data. Clin Ther 1998;20(suppl C):C40-C44.

Havey JM, Hill RE, Robins CW, et al. Supratherapeutic use of over-the-counter (OTC) analgesics by patients reporting to an urban dental clinic. J Toxicol Clin Toxicol 2001;39(5):543.

Hennekens CH, Buring JE. Epidemiology in Medicine. Boston: Little, Brown and Company, 1987:16-29.

Henrich WL, Agodoa LE, Barrett B, et al. Analgesics and the kidney: Summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an Ad Hoc Committee of the National Kidney Foundation. Am J Kidney Dis 1996 Jan;27(1):162-165.

Herzenberg LA, DeRosa SC, Dubs JG, et al. Glutathione deficiency is associated with impaired survival in HIV disease. Proc Natl Acad Sci USA 1997 Mar 4;94(5):1967-72.

Hickey RFJ. Chronic low back pain: A comparison of diflunisal with paracetamol. N Z Med J 1982;95:312-314.

Hoftiezer JW, O'Laughlin JC, Ivey KJ. Effects of 24 hours of aspirin, Bufferin, paracetamol and placebo on normal gastroduodenal mucosa. Gut 1982;23:692-697.

Jackson CH, MacDonald NC, Cornett JWD. Acetaminophen: A practical pharmacologic overview. Can Med Assoc J 1984 Jul 1;131:25-32.

Jewell SA, DiMonte D, Gentile A. Decreased hepatic glutathione in chronic alcoholic patients. J Hepatol 1986;3:1-6.

Johnson PC, Driscoll T. Comparison of plain and buffered aspirin with acetaminophen in regard to gastrointestinal bleeding. Current Therapeutic Research 1981 July;30(1):79-84.

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

Kampffmeyer HG. Failure to detect increased elimination rate of phenacetin in man after treatment with phenobarbitol. Klin Wehr 1969;1237-1238.

Kampffmeyer HG. Elimination of phenacetin and phenazone by man before and after treatment with phenobarbitol*. Eur J Clin Pharmacol 1971;3(2):113-118.

Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone Survey. JAMA 2002 Jan 16;287(3):337-344.

Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip: A randomised, double-blind, multi-center study. Pain 1990;43(3):309-318.

Koch-Weser J. Medical Intelligence: Drug Therapy. N Engl J Med 1976 Dec 2;295(23):1297-1300.

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

Kroner K, Hansen TB, Harving S, et al. Individually dosed codeine plus paracetamol versus paracetamol in long-treatment of chronic pain due to arthrosis of the hip: A randomised, double-blind, multicenter study. Acta Orthop Scand 1991;62(suppl 246):43.

Kuffner EK, Bogdan GM, Dart RC. Evaluation of hepatotoxicity in alcoholics from therapeutic dosing of acetaminophen. J Toxicol 1997;35(5):561.

Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: A randomized, double-blind, placebo-controlled trial. Arch Intern Med 2001 Oct 8;161(18):2247-2252.

Langman MJS, Weil J, Wainwright P, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994 April 30;343:1075-1078

Larson AM, Ostapowicz G, Fontana RJ, et al. Outcome of acetaminophen-induced liver failure in the USA in suicidal vs accidental overdose: Preliminary results of a prospective multi-center trial. Hepatology 2000;32(4 pt 2):396A.

Lauterberg BH. Analgesics and glutathione. Am J Ther 2002;9(3):225-233.

Lee WM. Acute liver failure. Clinical Perspectives in Gastroenterology 2001 Mar/Apr;101-110.

Lehmann JM, McKee DD, Watson MA, et al. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. J Clin Invest 1998 Sept; 102(5):1016-1023.

Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen: A practitioner-based randomized clinical trial. JAMA 1995 Mar 22/29;273(12):929-933.

Lequensne M, Fannius J, Reginster JY, et al. Floctafenin versus acetaminophen for pain control in patients with osteoarthritis in the lower limbs. Rev Rhumatis 1997;64(5):327-333.

Lieber CS. Cytochrome *P*-4502E1: Its physiological and pathological role. Physiol Rev 1997 Apr;77(2):517-544.

Lieber CS: Microsomal ethanol-oxidizing system (MEOS): The first 30 years (1968-1998) -- A review. Alcohol Clin Exp Res. 1999;23(6):991-1007.

Litovitz TL, Klein-Schwartz W, Caravati EM, et al. 1998 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1999 Sep;17(5):435-87.

Litovitz TL, Klein-Schwartz W, Dyer KS, et al. 1997 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1998 Sep;16(5):443-497.

Litovitz TL, Klein-Schwartz W, White S, et al. 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2000 Sep;18(5):517-574.

Litovitz TL, Klein-Schwartz W, White S, et al. 2000 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2001 Sep;19(5):337-395.

Litovitz TL, Smilken M, Felberg L, et al. 1996 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1997 Sep;15(5):447-500.

Lowenthal DT, Øie S, Van Stone JC, et al. Pharmacokinetics of acetaminophen elimination by anephric patients. J Pharmacol Exp Ther 1976;196(3):570-578.

Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterology 1995;109:1907-1916.

Makin A, Williams R. Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. Quarterly Journal of Medicine. 2000;93(6):341-349.

Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000 Mar;67(3):275-282.

Martin U, et al. The disposition of paracetamol and the accumulation of its glucuronide and sulphate conjugates during multiple dosing in patients with chronic renal failure. Eur J Clin Pharmacol 1991; 1:43-46.

Martin U, et al. The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis. Eur J Clin Pharmacol 1993;45:141-145.

Matsika MD, Moore N. Intentional drug overdoses: Validity of the information sources on drugs in comparison with plasma data. Thérapie 1999;54:273 (abstract).

Matts SGF, Boston PF. Paracetamol plus metoclopramide (Paramex) as an adjunct analgesic in the treatment of arthritis. Curr Med Res Opin 1983;8(8):547-552.

McGuinness BW, Lloyd-Jones M, Fowler PD. A double-blind comparative trial of Parazolidin and paracetamol. Br J Clin Prac 1969;23:452-455.

McMahon GT, McGarry K. Deliberate self-poisoning in an Irish county hospital. Ir J of Med Sci 2001;170(2):94-97.

McNeil Consumer Healthcare. NDA 19-872: Correspondence: APAP ADE Data 2000 December 20.

Miners JO, Atwood J, Birkett DJ. Determinants of acetaminophen metabolism: Effect of inducers and inhibitors of drug metabolism on acetaminophen's metabolic pathways. Clin Pharmacol Ther 1984 Apr;35(4):480-486.

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

Mitchell JR, Thorgeirsson SS, Potter WZ, et al. Acetaminophen-induced injury: Protective role of glutathione in man and rationale for therapy. Clin Pharmacol Ther 1974;16:676-684.

Miwa LJ, Jones JK, Pathiyal A, et al. Value of epidemiologic studies in determining the true incidence of adverse events: The non-steroidal anti-inflammatory drug story. Arch Intern Med 1997 Oct 13;157(18):2129-36.

Montague RE, Grace, RF, Lewis JH, et al. Urine drug screens in overdose patients do not contribute to immediate clinical management. Ther Drug Monit 2001;23(1):46-50.

Neuvonen PJ, Lehtovaara R, Bardy A, et al. Antipyretic analgesics in patients on antiepileptic drug therapy. Eur J Clin Pharmacol 1979;15:263-268.

O'Shea D, Davis SN, Kim RB, et al. Effect of fasting and obesity in humans on the 6-hydroxylation of chlorzoxazone: a putative probe of CYP2E1 activity. Clin Pharmacol Ther 1994 Oct;56(4):359-67

Ofman JJ, Maclean CH, Straus WL, et al. A metaanalyis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. J Rheumatol 2002;29(4):804-812.

Øie S, Lowenthal DT, Briggs WA, et al. Effect of hemodialysis on kinetics of acetaminophen elimination by anephric patients. Clin Pharmacol Ther 1975 Dec;18(6):680-686.

Olfson M, Marcus S, Druss B, et al. National trends in the outpatient treatment of depression. JAMA 2002;287:203-209

Omiecinski CJ, Remmel RP, Hosagrahara VP. Concise review of cytochrome P450s and their roles in toxicology. Toxicological Sciences 1999;48:151-156.

Ostapowicz G, Fontana RJ, Navarro VJ, et al. Use of liver transplantation in patients with acute liver failure. Hepatology 2000;32(4 pt 2):215A.

Parkinson A. Biotransformation of xenobiotics. In: Klaassen CD, ed. Casarett & Doull's Toxicology: The Basic Science of Poisons. 5th ed. New York: McGraw-Hill; 1996:113-186.

Perucca E, Richens A. Paracetamol disposition in normal subjects and patients treated with antiepileptic drugs. Br J Clin Pharmacol 1979;7:201-206.

Peura DA, Lanza FL, Gostout CJ, et al. The American College of Gastroenterology bleeding registry: Preliminary findings. Am J Gastroenterol 1997 Jun;92(6):924-928.

Pichard L, Fabre I, Fabre G, et al. Cyclosporin A drug interactions: Screening for inducers and inhibitors of cytochrome P-450 (cyclosporin A oxidase) in primary cultures of human hepatocytes and in liver microsomes. Drug Metab Dispos 1990;18:595-606.

Pohjola-Sintonen S, Kivisto KT, Vuori E, et al. Identification of Drugs ingested in acute poisoning: Correlation of patient history with drug analyses. Ther Drug Monit 2000;22(6):749-752.

Prescott L. Paracetamol: A critical bibliographic review. London: Taylor and Francis, Ltd;1996:231.

Prescott LF, Critchley JH, Balali-Mood M, et al. Effects of microsomal enzyme induction on paracetamol metabolism in man. Br J Clin Pharmacol 1981;12:149-153.

Prescott LF, Mattison P, Menzies DG, et al. The comparative effects of paracetamol and indomethacin on renal function in healthy female volunteers. Br J Clin Pharmacol 1990;29:403-412.

Prescott L, Speirs GC, Critchley JA, et al. Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. Eur J Clin Pharmacol 1989;36:291-297.

Price VF, Jollow DJ. Mechanism of decreased acetaminophen glucuronidation in the fasted rat. Biochem Pharmacol 1988;37(6):1067-1075.

Radu P, Atsmon J. Gilbert's Syndrome: Clinical and pharmacological implications. IMAJ 2001 August;3:593-598.

Report of CIOMS Working Group IV. Benefit-risk balance for marketed drugs: evaluating safety signals. 1998.

Rexrode KM, Buring JE, Glynn RJ, et al. Analgesic use and renal function in men. JAMA 2001 Jul 18;286(3):315-321.

Rost KL, Brösicke H, Brockmöller J, et al. Increase of cytochrome P450IA2 activity by omeprazole: Evidence by the ^{13}C-[N-3-methyl]-caffeine breath test in poor and extensive metabolizers of *S*-mephenytoin. Clin Pharmacol Ther 1992 Nov;52(2):170-180.

Rumack BH. Acetaminophen hepatotoxicity: The first 35 years. Clinical Toxicology 2002;40(1):3-20.

Sarich T, Kalhorn T, Magee S, et al. The effect of omeprazole pretreatment on acetaminophen metabolism in rapid and slow metabolizers of *S*-mephenytoin. Clin Pharmacol Ther 1997 Jul;62(1):21-28.

Sato C, Lieber CS. Mechanism of the preventive effect of ethanol on acetaminophen-induced hepatotoxicity. J Pharmacol Exp Ther 1981;218:811-815.

Schenker S, Speeg KV, Perez A, Finch J: The effects of food restriction in man on hepatic metabolism of acetaminophen. Clinical Nutrition 2001;20(2):145-150.

Schiodt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997;337:1112-1117.

Schmid R, Hammaker L. Glucuronide formation in patients with constitutional hepatic dysfunction (Gilbert's Disease). N Engl J Med 1959 June 25;260(26):1310-1314.

Seeff LB, Cuccherini BA, Zimmerman HJ, Adler E, Benjamin SB. Acetaminophen hepatotoxicity in alcoholics: a therapeutic misadventure. Ann Intern Med 1986;104:399-404.

Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: A view from the ARAMIS database. Am J Ther 2000;7:115-121.

Singh G, Fries JF. Famotidine to prevent peptic ulcer caused by NSAIDS. N Engl J Med 1996 Oct 24;335(17):1322-1323.

Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol Suppl 1999;26(56):18-25.

Skinner MH, Matano R, Hazle W, Blaschke TF. Acetaminophen metabolism in recovering alcoholics. Methods Find Exp Clin Pharmacol 1990;12:513-515.

Slone Epidemiology Unit. Prepared for McNeil Consumer Healthcare. Analgesic use in the adult population of the United States: Acetaminophen, aspirin, ibuprofen and naproxen. Results of a population-based telephone survey, 1998-2001. Report on file, 2001.

Sorenson HT, Mellamkjer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol 2000 Sep; 95(9): 2218-24.

Spielberg SP. Acetaminophen toxcity in lymphocytes heterozygous for glutathione synthetase deficiency. Can J Physiol Pharmacol 1985;63:468-471.

Spielberg SP, Gordon GB. Glutathione synthetase deficient lymphocytes and acetaminophen toxicity. Clin Pharmacol Ther 1981;29:51-55.

Spooner JB, Harvey JG. Paracetamol overdose: Facts not misconceptions. Pharm J 1993;252:706-707.

Stang PE, Fox JL. Adverse drug events and the Freedom of Information Act: An apple in Eden. Ann Pharmacother 1992 Feb;26(2):238-243.

Stein D, Peri T, Edelstein E, et al. The efficacy of amitriptyline and acetaminophen in the management of acute low back pain. Psychosomatics 1996;37(1):63-70.

Thummel KE, Slattery JT, Ro H, Chien JY, Nelson SD, Lown KE, Watkins PB. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. Clin Pharmacol Ther 2000;67(6):591-599.

Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. Annu Rev Pharmacol Toxicol 1998;38:389-430.

Tomlinson R, Young RP, Ng MCY, et al. Pharmacokinetics and disposition: Selective liver enzyme induction by carbamazeine and phenytoin in Chinese epileptics. Eur J Clin Pharmacol 1996;50:411-415

Triggs EJ, Nation RL, Long A, et al. Pharmacokinetics in the Elderly. Eur J Clin Pharmacol 1975;8:55-62.

Ullrich D, Sieg A, Blume R, et al. Normal pathways for glucuronidation, sulphation and oxidation of paracetamol in Gilbert's syndrome. Eur J Clin Invest 1987;17:237-240.

Villeneuve JP, Raymond G, Bruneau J, Colpron L, Pomier-Layrargues G. Pharmacokinetics and metabolism of acetaminophen in normal, alcoholic, and cirrhotic subjects. Gastroenterol Clin Biol 1983;7:898-902.

Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA 1994 Dec;272(23):1845-1850.

Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993;36(9):1196-1206.

Wright N, Prescott LF. Potentiation by previous drug therapy of hepatotoxicity following paracetamol overdosage. Scot Med J 1973; 18:56-58.

Wynne HA, Cope LH, Herd B, et al. The association of age and frailty with paracetamol conjugation in man. Age Ageing 1990 Nov;19(6):419-424.

Xiaodong S, Gatti G, Bartoli A. Omeprazole does not enhance the metabolism of phenacetin, a marker of CYPIA2 activity, in healthy volunteers. Ther Drug Monit 1994;16:248-250.

Zand R, Nelson SD, Slattery JT, et al. Inhibition and induction of cytochrome P4502E1-catalyzed oxidation by isoniazid in humans. Clin Pharmacol Ther 1993; 54:142-149.

Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995;22:767-773.

Section 5: Consumer Medication Use Behaviors

Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone Survey. JAMA 2002;287:337-344.

McNeil Consumer & Specialty Pharmaceuticals. MediScope medication-use/symptom diary data analysis. Data on file, 2002.

McNeil Consumer & Specialty Pharmaceuticals. McNeil OTC habits & practices study. Data on file, 2001.

National Council on Patient Information and Education (NCPIE). Attitudes and beliefs about the use of over-the-counter medicines: A dose of reality. 2002 January. (Available at http//:www.bemedwise.org/survey/final_survey.pdf. Access confirmed 23 July 2002.)

Slone Epidemiology Unit. Prepared for McNeil Consumer Healthcare. Analgesic use in the adult population of the United States: Acetaminophen, aspirin, ibuprofen and naproxen. Results of a population-based telephone survey, 1998-2001. Report on file, 2001.

Section 6: McNeil Initiatives and Recommendations

Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone Survey. JAMA 2002;287:337-344.

McNeil Consumer & Specialty Pharmaceuticals. McNeil OTC habits & practices study. Data on file, 2001.

Montauk SL, Rheinstein PH. Appropriate Use of Common OTC Analgesics and Cough and Cold Medications. American Family Physician Monograph No. 1. Leawood, KS: American Academy of Family Physicians, 2002.

Temple AR. Pediatric Dosing of Acetaminophen. Pediatric Pharmacology 1983;3:321-327.