methodologically flawed retrospective data from acetaminophen overdose cases to support proposed labeling recommendations that are designed to communicate information to consumers about the effects of taking therapeutic doses of acetaminophen (≤ 4 g/day).

- FDA's proposed labeling that "severe liver damage may occur if you take 3 or more alcoholic drinks every day while using this product" which defines the risk as one which can occur at recommended doses does not have a sound scientific basis.
    - It is inconsistent with known and theorized acetaminophen metabolism in the presence of alcohol.
    - It is not supported by new prospective data from multiple double-blind, randomized, placebo-controlled trials.

- Data do not support reducing the current maximum labeled daily dose of acetaminophen (4 g/day) for patients who consume any amount of alcohol. The data firmly support, when taken at therapeutic doses, up to the maximum labeled daily adult dose of acetaminophen (4 g/day), acetaminophen is a safe OTC analgesic and fever reducer for patients who consume alcohol.
- Alcohol use negatively affects decision-making, impairs judgment and memory, decreases risk perception, mars the ability to respond appropriately to potential threats, and is associated with an increased risk of death from virtually any type of injury.
    - The association of alcohol and acetaminophen-induced injury, such as acute liver failure, is related to risky behaviors that lead to acetaminophen overdose such as not reading and following acetaminophen dosing instructions, taking more than the recommended dose, suicide behavior, and not getting quick medical attention following an acetaminophen overdose.
    - Based upon the prospective data showing that alcoholics can safely take the maximum labeled daily dose of acetaminophen (4 g/day), it is much more likely that the reported association among alcohol, acetaminophen, and hepatotoxicity is related to acetaminophen overdose rather than to physiological conditions or metabolic alterations of acetaminophen metabolism in alcoholics.

- Alcohol use in association with acetaminophen overdose may be a risk factor for hepatotoxicity. Therefore, if FDA deems that an alcohol warning is necessary, this

warning should reflect the most current scientific data and reference acetaminophen overdose and not therapeutic doses of acetaminophen (≤ 4 g/day).

7.4 McNeil's Response to FDA's Critique of Prospective Studies Demonstrating the Safety of Therapeutic Doses of Acetaminophen in Alcoholics

Literature reviewed by FDA in the development of the December 26, 2006 proposed labeling included two references that describe prospective, randomized, double-blind, placebo-controlled clinical studies conducted at the Rocky Mountain Poison and Drug Center (RMPDC) which investigated the risk, if any, of hepatotoxicity following the use of therapeutic doses of acetaminophen for two days in newly abstinent chronic alcoholics [1,2]. FDA suggested that the studies had insufficient evidence to support the investigators conclusion that the daily maximum therapeutic dose of acetaminophen did not cause hepatic injury in alcoholics. Additional comments made by FDA with respect to these studies and McNeil's responses to those comments follow.

"A full report of this study (2-day pilot) is not available." [71 FR 77336]

- McNeil provides additional information and data from the Pilot Two-Day study within this section, including the synopsis of the study report.

"Neither study included an assessment of the quantity, frequency, and duration of alcohol use by the subjects. Alcoholic detoxification history and information on alcohol-related disorders, including more specific hepatic evaluations (such as hepatic CYP2E1 p450 enzymes levels, glutathione levels, or biopsy), were not reported. That information would have enabled a better evaluation of chronic alcohol use and underlying alcohol-induced liver abnormalities." [71 FR 77336]

- McNeil provides new data in this section that more fully characterizes alcohol use in the Two-Day studies that were available at the time of FDA's 2002 NDAC as well in the Three- and Five-Day studies that were not available. The historical and laboratory data demonstrate that nearly all the alcoholics enrolled in the studies were actively drinking, chronic heavy users of alcohol prior to entering the detoxification facility, that a representative cohort had lower-than-normal plasma glutathione levels, and based upon the alcohol history, would likely have CYP2E1 induction.

"Subjects with AST and ALT higher than 120 IU/L were excluded from the study, so no evaluation of subjects with underlying liver damage evidenced by slight elevations of liver function tests could be assessed. Such subjects may respond differently than those with more substantial hepatic impairment. Other investigators have similarly criticized the studies." [71 FR 77336]

- McNeil provides new data in which subjects with baseline AST and ALT up to 200 IU/L were studied. The inclusion of subjects with an AST and ALT up to 200 IU/L allowed between 87.8% to 95.3% of all alcoholics to be studied, instead of the 82.4% to 89.4% included when 120 IU/L was used as an exclusion criteria. Since there was no significant ALT, AST or INR differences between acetaminophen- and placebo-treated subjects who had an elevated ALT or AST at baseline, it is unlikely that inclusion of subjects with even higher AST or ALT levels would have led to different results.

"Assessing the change in liver function tests after drug administration may not adequately support a conclusion that the drug is without risk of liver injury in this population. If subpopulations of chronic alcoholics are sensitive to lower doses of acetaminophen, this type of study would be inadequate to make any assessment of risk." [71 FR 77336].

- McNeil disagrees with this statement. Hypothetically, if there is a potential risk of hepatic injury following therapeutic doses of acetaminophen newly abstinent alcoholics would be the "subpopulation" of chronic alcoholics at greatest potential risk within the first two days of ceasing alcohol consumption. During this short period, CYP2E1 is maximally induced, alcohol is not present to inhibit CYP2E1, and glutathione concentrations may be diminished. Since multiple double-blind, randomized, placebo-controlled studies conducted by multiple investigators at multiple detoxification sites in both the US and Canada have shown that the "subpopulation" with the greatest theoretical risk can safely take the maximum labeled daily doses of acetaminophen for multiple days, there is no reason to believe that any other "subpopulation" would be at any greater potential risk.

"FDA also finds that a 2-day treatment period may be too short to deplete the lowered hepatic glutathione capacity in the alcoholic people." [71 FR 77336]

- McNeil disagrees with the underlying supposition of this statement that assumes less-than-normal plasma concentrations of glutathione indicate a lowered hepatic glutathione capacity in alcoholic people to metabolize therapeutic doses of acetaminophen. There are no available scientific data in chronic alcoholics showing that hepatic glutathione can be depleted with therapeutic dosing, as true depletion is defined as an intracellular concentration below 10% of normal [3]. In contrast, prospective data in chronic alcoholics given a 2-g acetaminophen dose on the second day of abstinence, show the rates of glutathione consumption and repletion with acetaminophen metabolism were similar to control subjects even though baseline plasma glutathione concentrations were lower for the chronic alcoholic subjects [4]. In both groups, plasma glutathione concentrations reached a minimum at three hours after the acetaminophen dose and returned to baseline at the same time, and the amounts of glutathione consumed were nearly identical.

  Actively drinking newly abstinent alcoholics would be the "subpopulation" of chronic alcoholics most at risk because of maximal CYP2E1 induction, potentially reduced glutathione levels, and the absence of the protective effect of alcohol. The risk would be greatest during the first two days of acetaminophen administration when CYP2E1 would be maximally induced because of recent cessation of chronic alcohol use. In fact, as the length of alcohol abstinence increases, the potential risk of hepatic injury would decrease because CYP2E1 induction decreases with a half-life of 2.5 days following alcohol abstinence.

"The 2-day regimen cannot be extrapolated into the recommended 10-day dosing regimen in OTC drug product labeling." [71 FR 77336]

- As part of the RMPDC research program maximum labeled doses of acetaminophen, 4 g/day, were administered to newly abstinent alcoholics for up to five days and to adults with average ethanol consumption between one-to-three drinks per day for ten consecutive days without the development of hepatatoxicity, hepatic dysfunction, or hepatic failure.

"…the investigators gave no rationale for dosing acetaminophen for only 2 consecutive days while the drug is approved for 4 g/day for 10 consecutive days and commonly used for prolonged periods of time. " [71 FR 77336]

- The studies coordinated by RMPDC were part of a research program in which the safety of therapeutic doses of acetaminophen was demonstrated by administering maximum-labeled daily doses, 4 g/day, to alcoholics for treatment periods that steadily increased from two consecutive days (Pilot Two-Day and Two-Day study), to three consecutive days (Three-Day study), and ultimately to five consecutive days (Five-Day study). The RMPDC research program has also demonstrated the safety of maximum therapeutic doses of acetaminophen for ten consecutive days in actively drinking adults with average ethanol consumption between one to three drinks/day. Data from the Three-Day and Five-Day studies in chronic alcoholics and data from the Ten-Day study in actively drinking regular consumers of alcohol were not available at the time of FDA's 2002 NDAC meeting, so FDA has considered this new information in its justification for its proposed amendments to the TFM for OTC IAAA drug products.

"FDA concludes that these studies do not provide reliable evidence that people with chronic alcohol use can safely take 4 g/day of acetaminophen, particularly for up to 10 days in accordance with OTC drug product labeling." [71 FR 77336]

- McNeil disagrees with FDA's conclusion. New data from multiple double-blind, randomized placebo-controlled, clinical trials support the safety of the maximum therapeutic daily dose of acetaminophen, 4 g/day, in adults with an average ethanol consumption between one to three drinks/day and in alcoholics. Most of these data were not available at the time of FDA's 2002 NDAC meeting, so FDA has not taken this new information into consideration in its justification for its proposed amendments to the TFM for OTC IAAA drug products. These new data demonstrate that alcohol use is not a credible risk factor for the development of hepatic failure or hepatic dysfunction from true therapeutic doses of acetaminophen ($\leq$ 4 g/day).

"…the lack of elevation in liver enzyme values after only 2 days of acetaminophen lends little support to the author's conclusion regarding its safety in alcoholic people." [71 FR 77336]

- McNeil disagrees with this assessment. The RMPDC research program has demonstrated the safety of maximum-labeled daily doses of acetaminophen in chronic alcoholics by administering 4 g/day from two to five consecutive days. Hypothetically, if there is a potential risk of hepatic injury following therapeutic doses of acetaminophen, newly abstinent alcoholics would be the "subpopulation" of chronic alcoholics at greatest risk within the first two days of ceasing alcohol consumption. During this short period, CYP2E1 is maximally induced, alcohol is not present to inhibit CYP2E1, and glutathione concentrations may be diminished. The risk would be greatest during the first two days of acetaminophen administration when CYP2E1 would be maximally induced because of recent cessation of chronic alcohol use. In fact, as the length of alcohol abstinence increases, the hypothetical risk of hepatic injury would decrease since CYP2E1 induction decreases with a half-life of 2.5 days following alcohol abstinence. The RMPDC research program has also proven the safety of true maximum therapeutic doses of acetaminophen in actively drinking adults with average alcohol consumption between one to three drinks per day, by administering acetaminophen for ten consecutive days. The transaminase data from this study are consistent with data from acetaminophen trials in nondrinkers and non-alcoholics.

7.5 McNeil's Response to Other FDA's Comments

FDA's analysis of 282 cases from AERS noted, "For those cases with acetaminophen dose information, the mean dose associated with toxicity was lower for alcohol users compared to non-alcohol users." [71 FR 77321]

- Published data support that the true dose of acetaminophen ingested by a patient presenting for treatment is often unknown. When a dose is reported, data have demonstrated that patients often underestimate the dose taken. The reported daily dose of acetaminophen for individual cases does not represent the actual dose ingested, which is likely higher. In studies of drug overdose, involving multiple different medications including acetaminophen, there is a poor correlation between the reported dose of drug ingested and the measured drug level.

- Given alcohol's effects on memory, it is not surprising that analysis of the AERS database reported lower mean doses of acetaminophen associated with toxicity in reported alcohol users compared to non-alcohol users. Inaccurate and biased reporting in association with alcohol use is not uniquely associated with acetaminophen. The history obtained from intoxicated patients is more likely to be unreliable than the history obtained from nonintoxicated patients. Risk of injury also increases with the level of drinking, so it is not surprising that chronic alcoholics may be at increased risk of acetaminophen overdose compared to those who consume lesser amounts of alcohol.

"Risk factors, such as alcohol use or pre-existing liver disease, were identified and may have increased the risk for hepatotoxicity." [71 FR 77321] "Risk factors—multiple data sources identify alcohol and underlying liver disease as risk factors that may increase the potential for hepatotoxicity." [71 FR 77322] "Based on the data presented by Dr. Lee on liver failure, the experience in the University of Pennsylvania Hospital series, and data from the AERS database, FDA believes that alcohol users are a significant percentage of persons who develop severe liver injury." [71 FR 77336]

- McNeil agrees that a significant proportion of consumers who overdose on acetaminophen are users of alcohol. Alcohol use negatively affects decision-making, impairs judgment and memory, decreases risk perception, mars the ability to respond appropriately to potential threats, and is associated with an increased risk of death from virtually all types of injury. The association of alcohol and acetaminophen-induced injury, such as acute liver failure, is likely related to risky behaviors that lead to acetaminophen overdose such as not reading and following dosing instructions, taking more than the recommended dose, suicidal behavior, and not getting quick medical attention following an acetaminophen overdose.
- Based upon prospective data that support the safety of therapeutic doses of acetaminophen in alcoholics, and based upon alcohol's association with so many other forms of injury, it is much more likely that the association of alcohol, acetaminophen, and hepatotoxicity is related to risky behaviors that lead to acetaminophen overdose than to physiologic alterations that hypothetically affect acetaminophen metabolism in alcoholics.

"Acetaminophen products already have an alcohol warning to alert consumers of the risk for developing hepatotoxicity. It is important to determine whether the labeling should include a lower daily dose for chronic alcohol users." [71 FR 77336] "At this time, FDA is seeking both comments and data to support a specific dosage for acetaminophen as safe and effective in people who consume alcohol." [71 FR 77346]

- Data do not support reducing the current maximum labeled daily dose of acetaminophen for adults who consume any amount of alcohol. The results of multiple double-blind, randomized, placebo-controlled, clinical studies support the safety of the maximum labeled daily dose of acetaminophen, 4 g/day, in adults with an average ethanol consumption between one to three drinks/day and in alcoholics. When taken at therapeutic doses (≤ 4 g/day), acetaminophen is a safe OTC analgesic for patients who consume alcohol.

7.6 Limitations of Retrospective Data

Retrospective data cited by FDA in its proposed rule have suggested an association between acetaminophen, alcohol, and hepatotoxicity. It is well established that the vast majority of people who overdose on acetaminophen do not develop hepatotoxicity but that massive untreated acetaminophen overdose may result in hepatotoxicity [5]. Although the data are inconclusive as to whether alcohol use increases the risk of hepatotoxicity following acetaminophen overdose, the data do not support that alcohol use is a risk factor for hepatotoxicity with true therapeutic doses of acetaminophen (≤ 4 g/day) [6]. Retrospective data from case reports, case series, [7,8,9] and various databases such as AERS [10] and the Acute Liver Failure Study Group (ALFSG) cannot be used to determine if alcoholics or patients who drink alcohol are at risk of hepatotoxicity from therapeutic doses of acetaminophen or if alcohol affects the outcome following acetaminophen overdose.

Conclusions derived from flawed retrospective data, such as the FDA's analysis of cases of hepatotoxicity associated with acetaminophen and Lee's analysis of data from the ALFSG, should be viewed with appropriate skepticism. This is especially true with respect to the actual dose of acetaminophen that may have caused hepatotoxicity and with respect to differences in outcomes in subsets of patients, such as users of alcohol and alcoholics [11]. Critical flaws inherent to the AERS reporting system and the ALFSG's methodology severely limit the validity of hypotheses attributed to such data [12,13]. The published literature upon which the FDA analysis in the proposed rule was based did not meet the

most basic of accepted methodological standards designed to minimize inaccuracies, imprecision, inconsistencies, and bias [11].

In light of new prospective data from double-blind, randomized, placebo-controlled studies that support the safety of the maximum-labeled daily dose of acetaminophen (4 g/day), it is inappropriate for FDA to use historical methodologically flawed retrospective data from acetaminophen overdose cases to support proposed labeling recommendations that are designed to communicate information to consumers about the effects of taking therapeutic doses of acetaminophen (≤ 4 g/day).

7.6.1 Problems with Using Inaccurate, Imprecise and Incomplete Information

Drug histories, especially with respect to acetaminophen, are often unreliable [14,15]. In most instances, it is virtually impossible to retrospectively determine the actual dose of acetaminophen ingested. FDA acknowledges that "dosing information may be unreliable" [71 FR 77321] and that the "actual dose ingested can be difficult to ascertain" [71 FR 77321]. Published data support that the true dose of acetaminophen ingested by a patient presenting for treatment is often unknown [16]. When a dose is reported, data have demonstrated that patients often underestimate the dose taken [17]. The reported daily dose of acetaminophen for individual cases does not represent the actual dose ingested, which is likely higher. In studies of drug overdose, involving multiple different medications including acetaminophen, there is a poor correlation between the reported dose of drug ingested and the measured drug level [18].

The reported involvement and dose of acetaminophen, alcohol, and other drugs that healthcare professionals obtain from patients, family members, close contacts and medical personnel is potentially unreliable [19,20]. Reports alleging that an alcoholic developed hepatic injury associated with acetaminophen use often involve doses of acetaminophen reported to be greater than the maximum labeled adult daily dose. Review of these data often reveals evidence of inaccurate dosing history, often supported by acetaminophen levels more consistent with overdose [8,9,21,22].

Dose is even more difficult to determine in alcoholic patients and in persons who may be intoxicated. Chronic alcoholics, drug overdose patients, and intoxicated patients often cannot provide a reliable history of the medications or amounts they have taken [23,24,25,26]. Alcohol affects memory and cognition and alcoholics have both short-term and long-term memory impairment [27]. Memory abnormalities and differing degrees of

amnesia in alcoholics and intoxicated patients specifically call into question the reliability of reported dose information in association with alcohol use [28,29].

Inaccuracies may also occur when healthcare professionals document in the medical record and forward information to manufacturers and regulatory agencies. Using videotaped and directly observed medical encounters it has been established that written records are often incorrect when compared with the actual data that was presented [30].

Documented medical information is often ambiguous with different healthcare professionals recording conflicting information that describes the same patient. Inconsistent coding, inaccurate categorization, and non-uniform handling of uncertain or missing data also occur [11]. It is often unclear if recorded negative responses indicate that a feature was truly absent or just not recorded [31]. When investigators are well informed about the study hypotheses or have preconceived expectations, the categorization, presentation, and interpretation of the data may be biased [31,32]. Interpretation of retrospective data is often limited by other biases such as recall, observer, referral, and reporting.

7.6.2 Lack of Methodological Standards

FDA's analysis of hepatotoxicity cases reportedly associated with acetaminophen and alcohol lacks confirmation that it conformed to accepted methodological standards for conducting and reporting such analyses. Such standards include (i) explicit protocols for case selection and exclusion, (ii) abstractor training, (iii) clear predetermined definitions of important variables (how dose and duration of acetaminophen and alcohol is to be determined or specific definitions for "intentional" and "unintentional" classification), (iv) blinding of chart reviewers to the hypotheses being tested and group assignments, (v) assessment of interrater reliability and use of standardized abstraction, and (vi) coding forms designed to promote more uniform handling of data, especially data that are conflicting [33]. In addition, most of the published literature also do not include a clear description of sampling methodology (ie, convenience, consecutive, systematic, or random), a discussion of how missing data or incomplete data were handled, whether IRB approval was obtained, a declaration of the authors conflicts of interest, or a disclosure of funding sources [34,35].

7.6.3 Attempting to Classify Intent Does Not Improve the Accuracy of Determining the True Dose of Acetaminophen Ingested

Most of the retrospective data do not make the critical distinction between a true therapeutic dose and ingestion of an overdose. Although potentially helpful in guiding efforts to prevent acetaminophen overdose, poorly defined terms such as "therapeutic intent" [8], "therapeutic misadventure" [22] "accidental", "unintentional" and "intentional" are unimportant when attempting to determine the true dose ingested. Classification of intent does not improve the accuracy of determining the true dose of acetaminophen ingested and cannot determine whether or not outcome following acetaminophen overdose is impacted by the use of alcohol or whether or not a true therapeutic dose of acetaminophen can cause hepatotoxicity.

Classification of intent by assigning these terms can be influenced by external factors, including what is documented within the medical record with respect to the psychiatric history, psychiatric complaints, and medications used to treat psychiatric conditions. Moreover, the classification of intent may be influenced by the fact that psychiatric complaints and illnesses may be omitted in up to one-third of records of clinical encounters [36]. For example, given the social stigma associated with suicide behaviors and its implications, intentional overdoses may be erroneously reported within the medical record. Classifying cases based upon intent has the potential to introduce bias and influence how dosage information is recorded, reported, and interpreted while contributing nothing to the reliability of dose information.

7.7 Data Assessing Whether Alcoholics May Be At Increased Risk For Hepatotoxicity Following Acetaminophen Overdose

7.7.1 Retrospective Data From Published Studies

There are conflicting, retrospective human data on how the presence of alcohol may affect the risk of developing hepatotoxicity following acute intentional or repeated supratherapeutic acetaminophen overdose. The acute* ingestion of alcohol in conjunction with an acetaminophen overdose has been reported to decrease the risk of hepatotoxicity [37,38,39,40,41], and to have no effect on the risk of hepatotoxicity [18,42,43]. There are also conflicting, retrospective human data on how chronic∞ ingestion of alcohol before an acetaminophen overdose may affect the risk of developing hepatotoxicity [18,20,21,37,38,40,41,42,43,44,45,46,47]. Chronic ingestion of alcohol before an

* presence of alcohol in a patient's system at the time of an acetaminophen overdose
∞ regular ingestion of alcohol for a period of time before an acetaminophen overdose

acetaminophen overdose has been reported to have no effect on the risk of hepatotoxicity [18,20,42,45] and to increase the risk of hepatotoxicity [37,38,43,44]. Even within some studies, the data are conflicting [22,40]. For example, in the largest case series of acute acetaminophen overdose, a history of chronic alcohol abuse or alcoholism was not associated with increased hepatotoxicity among low risk cases with reported acetaminophen level below the four hour post-ingestion 200-µg/mL line on the nomogram or NAC started within eight hours post-ingestion. Instead, it was associated with increased hepatotoxicity among the high-risk group with reported acetaminophen level above the four hour post-ingestion 300-µg/mL line [48].

Interpretation of how alcohol use may or may not affect a patient's outcome following acetaminophen overdose is difficult because imprecise, poorly defined terms are often used to describe the dose and duration of both the acetaminophen use and the alcohol use and the timing of the alcohol and acetaminophen ingestions in relation to each other. Examples of terms used in some of these reports to describe duration of drug exposure include "acute"[21,37,38,40], "chronic" [21,37,38], "single time point" [20], "over a period of time" [20], "both acute and chronic alcohol intake" [38], "chronic intake but no acute alcohol intake" [38], and "both acute and chronic combined ingestion of alcohol" [37].

Examples of terms used in some of the studies to describe the timing of alcohol and acetaminophen ingestions in relation to each other include "concurrent intoxication"[21], "concurrent ingestion" [41], "concomitant acute alcohol" [37], "acute alcohol intake concomitantly with paracetamol but without chronic intake" [38], "ingestion of alcohol as part of the intoxication in excess of the patient's regular daily consumption" [37], "prior alcohol consumption" [42], "simultaneous ingestion of alcohol with paracetamol" [42], and "considerable quantities of alcohol had also been consumed at the time of the overdose" [45]. Imprecise and poorly defined terms like these are one explanation for why there are conflicting data with respect to how alcohol use may or may not affect the development of hepatotoxicity following acetaminophen overdose.

Using retrospective data in an attempt to determine if alcohol affects the outcome following acetaminophen overdose is problematic because many essential data are either captured inaccurately or not captured at all including the:

- true dose of acetaminophen and alcohol ingested [6,20,21]
- actual elapsed time between acetaminophen and alcohol ingestion and presentation to a healthcare facility [6,21,40,42,45]
- true duration of acetaminophen and alcohol use at the specified dose
- blood alcohol level at the time of acetaminophen overdose
- elapsed time between ingestion and treatment with antidote [18,40,42]
- presence or absence of other coingestants [49]
- the underlying health of the patient at the time of the overdose
- the appropriateness of the treatment rendered [50]

Although some retrospective data suggest that alcohol use may increase the risk for hepatotoxicity following acetaminophen overdose, the use of inaccurate and/or inconsistent terminology to describe crucial temporal relationships makes meaningful comparisons across studies difficult [18,37,42,44].

7.7.2 Alcohol Use Is Associated With An Increased Risk of Death From Virtually Any Type of Injury

7.7.2.1 Retrospective Human Data Presented at FDA's 2002 NDAC Meeting

FDA says that based upon the data presented at the 2002 NDAC meeting from the ALFSG, the experience in the University of Pennsylvania Hospital series, and data from the AERS database, that alcohol users are a significant percentage of persons who develop severe liver injury. This conclusion appears to be based upon: (1) percentages of cases in which alcohol use or alcohol abuse was reported and (2) upon the finding of a lower reported mean dose of acetaminophen in reported alcohol users compared to the reported dose in reported non-users of alcohol in the FDA's analysis of AERS.

Alcohol use was reported in 57% of the cases and alcohol abuse was reported in 19% of the cases from the ALFSG [51]. Alcohol use was reported in 61-87% and 41% of the cases from the University of Pennsylvania Hospital series and from the AERS database, respectively. These percentages are not surprising and are consistent with what has been reported in the medical literature with respect to patients presenting with virtually any type of injury, including drug overdose, in association with alcohol use [51,52,63,53,54].

It is well established that alcohol use negatively affects memory, decision-making, judgment, risk perception, and the ability to respond appropriately to potential threats [55,53]. Alcohol use is a risk factor for increased injury severity and is associated with fatal injuries [52]. Alcohol use is associated with practically all types of injuries and is a characteristic of 40% to 60% of motor vehicle accident victims, 32% to 46% of homicide victims, 20% to 50% of suicide victims, 25% to 50% of drowning victims and 40% to 64% of fire and burn victims [52,53,56,57]. Alcohol use has also been reported in 30% to 50% or more of drug overdose deaths not specifically attributable to acetaminophen [58]. Presenting to an emergency department with alcohol intoxication is a potential independent risk factor for premature death [59]. The data presented at FDA's NDAC meeting confirms the involvement of alcohol as a risk factor for acetaminophen overdose and drug-related injury.

Risk of injury also increases with the level of drinking, so it is not surprising that chronic alcoholics may be at increased risk of acetaminophen overdose compared to those who consume lesser amounts of alcohol. Using NHANES data, a dose-response relationship was shown between the usual number of drinks consumed per occasion and the risk of fatal injury. Persons who consumed five or more drinks per occasion are nearly twice as likely to die from injuries than persons who drank fewer than five drinks per occasion. Persons who consume nine or more drinks per occasion are more than three times as likely to die from such injuries. This dose-response relationship is also seen when chronic alcoholics experience hepatic injury from acetaminophen overdose [54,60,61].

Given alcohol's effects on memory and the ability to provide an accurate history, it is not surprising that with regard to doses reported, analysis of the AERS database reported lower mean doses of acetaminophen associated with toxicity in cases involving alcohol users than in cases involving non-users. Inaccurate and biased reporting because of alcohol use is not a phenomenon that is unique to cases of acetaminophen overdose. [62]. A history obtained from an intoxicated patient in any setting is less likely to be reliable than a history obtained from a sober patient.

Alcohol use can also lead to a multitude of risky behaviors such as not following acetaminophen dosing instructions, taking more than the recommended dose, suicidal behavior, and not getting quick medical attention following an acetaminophen overdose [20,42,45,63,64,65]. Therefore, acetaminophen overdose may be accompanied by alcohol use, but the morbidity and mortality is not necessarily the result of alcohol-induced

alterations in physiology or acetaminophen metabolism. Based upon alcohol's association with so many other forms of injury, it is much more likely that the association between alcohol, acetaminophen, and hepatotoxicity at purportedly therapeutic doses is related to risky behaviors that lead to acetaminophen overdose rather than to physiologic alterations that may hypothetically affect acetaminophen metabolism in alcoholics or people who drink. Alcohol's association with acetaminophen overdose is consistent with the fact that daily drinking, binge drinking, and heavier drinking have been associated with virtually all other forms of injury [56].

7.7.2.2 The Association of Alcohol Abuse and Alcohol Intoxication with Suicide and Suicide Attempts

Alcohol is the substance most frequently associated with suicide and suicide attempts. [65] Alcoholism is associated with increased risk of both completed suicide and of suicide attempts. Estimates of the lifetime risk of suicide in alcoholics vary widely, from 3.4% to 15%, but clearly there is increased risk in comparison to the general population.

Alcoholics who die by suicide are likely to have co-morbid psychiatric illnesses, especially depression [66]. Data analyzed from the ECA survey indicated active alcoholics were eight-teen times more likely to make a suicide attempt than the general population [67]. Additionally, alcohol intoxication also seems to play a role in suicide risk for both alcoholics and for non-alcoholics. Autopsy studies have shown positive blood alcohol levels in 20% to 50% of suicides [68,69].

Intoxication is also associated with lower likelihood of seeking help before death. Suicide attempts involving alcohol are more likely to be impulsive. In one study of acutely intoxicated alcoholics the majority of subjects either didn't remember the reasons for their attempt or they had made the attempt on a sudden impulse [70]. The American Psychiatric Association Guideline concludes, "Thus, alcohol consumption may make intervention more difficult by simultaneously limiting the communication of intent [69,71], increasing impulsivity, decreasing inhibition, and impairing judgment [72]." One study of completed suicides found that alcohol misusers were more likely to have died from an overdose of medications [64]].

Alcohol intoxication is also associated with about one-third of suicide attempts, according to several studies [73,74,75]. Consumption of alcohol was found in 41% of those who attempted suicide by overdose [75].

7.7.3 Prospective Data

Ethical considerations preclude the prospective study of hepatotoxic overdoses of acetaminophen and clinical outcomes with and without acute or chronic alcohol use. However, prospective studies have demonstrated the safety of therapeutic doses of acetaminophen in chronic alcoholics and those who drink on average between one and three drinks per day. Therefore, if FDA deems that an alcohol warning is necessary, this warning should apply only to acetaminophen overdose (> 4 g/d) and not to therapeutic doses of acetaminophen (≤ 4 g/day) where the prospective data demonstrate the safety of acetaminophen.

7.8 Administration of Therapeutic Doses of Acetaminophen to Chronic Alcoholics and Regular Drinkers Who Consume on Average Less Than 3 Alcoholic Drinks Per Day

7.8.1 Retrospective Data

Case reports, cases series [7,8,9], and analysis of retrospectively collected information from some databases, such as AERS, have been interpreted to show an association between acetaminophen, alcohol, and hepatotoxicity. As noted above, retrospectively collected data cannot be used to determine whether a true therapeutic dose of acetaminophen causes hepatic injury in a patient reported to drink any amount of alcohol.

A systematic review of the published literature over a 23-year period, found 25 patients in 20 reports that developed hepatic injury in association with the reported use of therapeutic doses of acetaminophen by an alcoholic patient. The authors noted severe weaknesses in these reports including conflicting data, insufficient reported data to reach a conclusion, reports of amounts and timing of acetaminophen ingestion that were likely inaccurate, potential misattribution of acetaminophen as the cause of hepatic injury, assumption that elevated aminotransferase levels are caused only by acetaminophen toxicity and acetaminophen levels that clearly suggest large acetaminophen overdoses. Only five of these cases contained enough information to suggest involvement of acetaminophen and did not include data that questioned the attribution to acetaminophen [76]. Even in these cases, causality could not be attributed to acetaminophen. This highlights the limitations of retrospective data and the need for prospective studies designed to determine if alcoholics and occasional drinkers, who regularly consume alcohol, can safely take maximum labeled doses of acetaminophen.

A systematic review of all prospective studies that have used acetaminophen in a wide variety of patient groups, identified 30,865 patients who received acetaminophen for more than one day (median duration of ingestion five days). Several studies included alcoholic patients and many others did not exclude alcohol consumption in the subjects enrolled. Despite the inclusion of many purportedly high risk patients, including alcoholic patients and patients with liver disease, there were no reports of acute liver failure or death from acetaminophen [77].

7.8.2 Prospective Data from Pharmacokinetic/Metabolism Studies Do Not Suggest a Risk of Therapeutic Doses of Acetaminophen in Alcoholics

Pharmacokinetic and metabolism studies of acetaminophen in chronic alcohol abusers are reviewed in Item 1, Section 5, Characterization Liver Safety: The Role of Acetaminophen Metabolism. Available evidence from chlorzoxazone metabolism data in nondrinking adults and alcohol abusers suggests that there is about a one-to-two day window after alcohol is removed from the blood when CYP2E1 activity is increased. In a study [78] of healthy adults examining the effect of alcohol induction on acetaminophen metabolism immediately after alcohol was cleared, the fraction of the acetaminophen dose converted to NAPQI, and indirectly measured as detoxified urinary cysteine and mercapturic conjugates, was modestly increased by 21.6% ($p < 0.03$). While supporting the operational mechanism, the increase from 7.5% to 9.2% in the fraction of dose excreted as total thiols is clinically insignificant, causing no additional risk of acetaminophen hepatotoxicity at therapeutic doses in adults who are moderate or occasional binge drinkers of alcoholic beverages.

Several clinical metabolism studies [4,79,80,81,82,83] have been conducted comparing the biotransformation of acetaminophen between nondrinking control subjects and chronic alcoholics after ceasing alcohol consumption. Overall, the fact that there are no, or only fairly small, changes in thiols produced within the first few days after ceasing alcohol consumption shows that the effect of alcohol on acetaminophen oxidation by CYP2E1 induction is moderate at best. These data provide metabolic evidence that chronic alcoholics are not at risk of hepatotoxicity with therapeutic doses of acetaminophen

7.8.3 New Prospective Data from Double-Blind Randomized Placebo Controlled Trials Demonstrate the Safety of Maximum Therapeutic Doses of Acetaminophen (3.9g and 4g/d) in Chronic Alcoholics

Five prospective, randomized, blinded, placebo-controlled studies have been completed in which maximum daily doses of acetaminophen were administered for up to five days to over 400 newly abstinent chronic alcoholics [1,2,84,85,86]. Four of these studies were coordinated by the Rocky Mountain Poison and Drug Center (RMPDC) as part of a step-wise research program investigating the potential interaction of acetaminophen and alcohol in chronic alcoholics [1,2,84,85]. The fifth study, available as an abstract, was conducted by Bartels and colleagues in Canada and was similar in design to the studies conducted at RMPDC [86]. These studies are summarized in Table 7-1, and additional written synopses, made available by RMPDC for its studies, are located behind the available publication.

In these studies, actively drinking chronic alcoholics were abruptly withdrawn from their daily alcohol intake and were administered the maximum daily dose of acetaminophen, 3.9 [86] and 4 grams, [1,2,84,85], at the time of maximum theoretical vulnerability. Purportedly at this time, CYP2E1 would have been fully induced and ethanol would not be present to inhibit the formation of NAPQI by CYP2E1. Data from the three longer studies were not available at the time of FDA's 2002 NDAC meeting and directly address FDA's concerns in its 2006 proposed rule that "a 2-day treatment period may be too short to deplete the lowered hepatic glutathione capacity in the alcoholic people." [71 FR 77336]

7.8.3.1 Study Objectives

7.8.3.1.1 Primary Objective

All of the studies were designed to evaluate if maximum therapeutic doses of acetaminophen (3.9-4 g/d) cause hepatotoxicity, hepatic dysfunction or hepatic failure in alcoholic patients. Acetaminophen was administered for two consecutive days in two studies [1,2] and for three [84], four, [86] and five [85] consecutive days in three additional studies.

7.8.3.1.2 Secondary Objectives

Additional analyses were performed in many of the studies and included measurements and analysis of (1) subjects with an AST/ALT ratio of greater than 2.0 which has been used as a definition of alcoholic liver disease, (2) subjects with an elevated baseline ALT greater than 40 IU/L, (3) subjects positive for hepatitis C virus antibody, (4) subjects with evidence of clinical malnutrition, and (5) subjects who received CYP2E1 substrates, inducers, or

inhibitors. The effect of acetaminophen on plasma concentrations of reduced glutathione was also investigated versus baseline concentrations.

7.8.3.2 Study Design for Pilot Two-Day, Two-Day, Three-Day and Five-Day Studies

The study designs of the prospective studies are summarized in Table 7-2. All of the studies were randomized and placebo-controlled [1,2,84,85,86]. In the Pilot Two-Day, Two-Day, and Five-Day studies, the randomization of acetaminophen to placebo was 1:1 [1,2,85]. In the Three-Day study the randomization of acetaminophen to placebo was 2:1 [84]. The Pilot Two-Day, Two-Day and Four-Day studies were single-center studies [1,2,86] while the Three- and Five-Day studies were each conducted at two independent sites [84,85]. The four studies conducted at RMPDC [1,2,84,85] were double-blind and the study conducted by Bartels and colleagues [86] was triple-blind.

In all of the studies, the maximum therapeutic daily dose of acetaminophen was studied. In the studies coordinated by the RMPDC acetaminophen 1 g was administered every four hours for four times daily, for a total of 4 g/d [1,2,84,85]. In the study by Bartels and colleagues [86], 1.3 g of sustained release acetaminophen was administered every eight hours for a total of 3.9 g/d.

These prospective studies were specifically designed to safely maximize the opportunity to detect a potential interaction between maximum daily doses of acetaminophen and alcohol for consecutive days during the period of maximal vulnerability. This period of maximum vulnerability lasts from the time that alcohol is eliminated from the body of an chronic alcoholic to the time that CYP2E1 induction has waned. Consequently, the conditions in these studies mimic those commonly cited in reports of acetaminophen injury associated with reported therapeutic doses of acetaminophen in the medical literature, namely induction of CYP2E1 and with concomitant lower levels of glutathione [8,9,87].

Because alcohol is a substrate for CYP2E1 and would compete with acetaminophen metabolism, these studies did not include alcoholics who continued to ingest alcohol during the time of acetaminophen administration. Acute ingestion of alcohol at the time of acetaminophen dosing competitively inhibits rather than increases NAPQI formation. Based upon metabolic theory and pharmacokinetic data [88,89], it is more likely that continued alcohol consumption would decrease rather than increase the susceptibility of alcoholic patients to acetaminophen-related hepatic injury.

In these studies, acetaminophen or placebo was initially dosed shortly after actively drinking chronic alcoholics presented to a detoxification facility and abruptly discontinued chronic alcohol consumption. If there could be a risk of hepatic injury following administration of therapeutic doses of acetaminophen, the subpopulation of actively drinking chronic alcoholics may be hypothetically more at risk during the time immediately after ceasing alcohol consumption. Based on theory, this subpopulation of chronic alcoholics is supposedly vulnerable because (1) CYP2E1, the enzyme that converts acetaminophen to its toxic metabolite, would be maximally induced at this time [88]; (2) alcohol is not present in the blood to inhibit CYP2E1 metabolism of acetaminophen [39,78,90]; and (3) hepatic glutathione concentrations would be expected to be low due to chronic active alcohol consumption [4,91]. Moreover, CYP2E1 induction, which has a half-life of 2.5 days following cessation of chronic active alcohol intake, would not yet have begun to wane [92,93]. The hypothetical risk of hepatic injury would be greatest during the first two days of acetaminophen therapy. As the length of alcohol abstinence increases, the hypothetical risk of hepatotoxicity would be expected to decrease as CYP2E1 induction wanes [92,93,94].

All of these studies were designed to detect hepatotoxicity that may have developed within one to two days following discontinuation of acetaminophen dosing, a time period that would be expected to detect acetaminophen-related hepatic dysfunction and hepatic failure in the unlikely event that it were to develop following discontinuation of multi-day acetaminophen dosing.

7.8.3.3 Study Population

7.8.3.3.1 Characterization of Baseline Hepatic Testing in Study Population

The prospective studies varied in the exclusion criteria used for ALT and AST, Table 7-3. In the Pilot Two-Day study [1] and the Two-Day study [2], subjects were excluded if their baseline serum AST or ALT was above 120 IU/L or if their baseline INR was >1.5. However, in the Three-Day and Five-Day studies, the exclusion criteria were modified to include subjects with higher AST and ALT levels; subjects were excluded if their baseline serum AST or ALT was above 200 IU/L or if their baseline INR was >1.5 [84,85]. Therefore, the studies conducted since FDA's 2002 NDAC meeting have addressed FDA's concern stated in its proposed rule that subjects with baseline transaminase elevations were inadequately addressed [71 FR 77336].

Based on these criteria, 17.6% and 10.6% of screened subjects were excluded from the Pilot Two-Day and the Two-Day study, respectively, because of an AST or ALT > 120 IU/L. However, only 4.7% and 12.2% of screened subjects were excluded from the Three-Day and Five-Day studies, respectively, because of an AST or ALT > 200 IU/L. These studies included the vast majority of alcoholics presenting for alcohol detoxification. However, alcoholics and patients with alcoholic liver disease may or may not have elevated hepatic aminotransferase enzyme activity, so the absolute degree of enzyme elevation does not necessarily provide much insight into the severity of underlying alcohol-related liver disease [75,95]. Therefore, it is unlikely that subjects with higher AST or ALT activity would respond differently to acetaminophen.

In each study coordinated by the RMPDC, baseline values for AST, ALT, INR, alkaline phosphatase, total bilirubin, total protein, and albumin were determined and the results are listed in Table 7-4. In the study conducted by Bartels and colleagues [86], AST, ALT, INR, and alpha-glutathione-S-transferase levels were analyzed at baseline. However, no baseline values were reported in the abstract.

FDA noted that baseline hepatic CYP2E1 p450 enzyme levels were not assessed in both Two-Day studies and that such information would have enabled a better evaluation of chronic alcohol use and underlying alcohol-induced liver abnormalities. Baseline CYP2E1 activity was not measured in any of these prospective studies. However, based on pharmacokinetic data and the history of active alcohol consumption in the chronic alcoholics enrolled in the studies RMPDC coordinated, Table 7-5, one would expect that at baseline, hepatic CYP2E1 activity would be maximally induced. Human studies have shown that chronic alcohol consumption results in an approximately two-fold increase in CYP2E1 activity using chlorzoxazone as a probe [93], although neither the quantity of alcohol or duration of active alcohol intake that is required to maximally induce CYP2E1 activity was reported. One study suggests that increased CYP2E1 activity begins immediately upon exposure to alcohol [89]. CYP2E1 activity would then be expected to decline steadily over the course of the acetaminophen treatment period from the first dose of study drug until the last, two to five days later. Human studies have shown that following alcohol abstinence, the half-life for CYP2E1 induction is approximately 2.5 days and that CYP2E1 activity returns to normal within three to eight days of discontinuing chronic alcohol intake [92,93,94].

FDA noted that baseline biopsies were not conducted in the two Two-Day studies and that such information would have enabled a better evaluation of chronic alcohol use and

underlying alcohol-induced liver abnormalities. For ethical reasons, liver biopsies were not performed in any of the studies described in Table 7-1. Investigators from the RMPDC indicated that they did not perform liver biopsies, because they were not needed for clinical management and as such they deemed such a practice unethical due to the inherent risks associated with conducting these procedures.

7.8.3.3.2 Characterization of Alcohol Use in Study Population

All five of the prospective studies enrolled alcoholics who were actively drinking chronic heavy users of alcohol at presentation and who had abruptly discontinued alcohol intake upon entering a detoxification facility.

Contrary to FDA's statement in its proposed rule that "Neither study included an assessment of the quantity, frequency, and duration of alcohol use by the subjects.," both of the Two-Day studies, as well as the Three- and Five-Day RMPDC studies, thoroughly assessed alcohol use in all subjects by obtaining a detailed history and using a standardized validated questionnaire which is a reliable and reproducible method of collecting information on alcohol use [96]. The RMPDC studies specifically included completion of the CAGE questionnaire and Brief Michigan Alcoholism Screening Test (MAST) (Table 7-5), a self-assessment of alcoholism (Table 7-6), baseline serum γ-glutamyl transferase (GGT) levels (Table 7-8), baseline AST/ALT ratio (Table 7-9), an assessment of the duration of alcohol use/alcoholism (Table 7-10 and Table 7-11), and determination of breath/blood alcohol levels (Table 7-12).

The CAGE questionnaire is a widely used validated screening instrument for alcoholism [97]. Different studies have found different sensitivities and specificities of the CAGE questionnaire in screening patients for alcohol abuse and/or dependence in primary care settings. When the cutoff is set at two or more positive responses, sensitivities ranged from 21% to 94% and the specificity ranged from 77% to 97% [98]. Individuals who have two or more positive responses are considered likely alcoholics. All individuals who were enrolled in the studies coordinated by RMPDC completed the CAGE (Table 7-5). Almost all subjects had positive responses to at least two of the CAGE questions and more than half of the subjects had positive responses to all four questions increasing both sensitivity and specificity. Results of the CAGE questionnaire support that the subjects within the RMPDC coordinated studies were true alcoholics.

The Brief MAST is another validated screening questionnaire for the detection of alcoholism [99]. This tool has nine self-assessment questions about alcohol use. All individuals who were enrolled in the studies at RMPDC completed the Brief MAST. As shown in Table 7-5, almost all subjects had positive responses to at least six of the Brief MAST questions and mean Brief Mast scores ranged from 21.7 to 23.5.

In the study in which acetaminophen was administered for five days, alcohol dependence and abuse were evaluated using the DSM-IV criteria. Based on these criteria, 138 (97%) subjects were alcohol dependent. Of the four subjects that did not meet the criteria for alcohol dependence 3 (2%) were alcohol abusers. Only one patient did not meet the criteria for alcohol dependence or abuse. All subjects who participated in the Two-, Three-, and Five-Day RMPDC studies were specifically asked: “Are you an alcoholic?” As shown in Table 7-6, almost all of the subjects who participated in these studies stated that they were alcoholics.

There is no blood test that can be used to diagnose alcoholism, and no one blood test that can diagnose alcoholic liver disease [100]. AST and ALT perform poorly as screening tools for alcoholism [101]. Although elevated serum γ-glutamyl transferase (GGT) activity has been reported to be less sensitive than the Brief MAST for detecting alcoholism, it may also be used to support a diagnosis of alcoholism. GGT activity generally rises after several weeks of heavy alcohol intake (ie, 70 drinks/week) and returns to normal after two to six weeks of abstinence [102]. It is recommended that GGT measurement be used along with self-report screening measures for alcoholism [102]. The Pilot Two-Day, Two-, Three-, and Five-Day studies evaluated GGT levels at baseline, Table 7-7. As shown in Table 7-8, across all four studies, 81 subjects had a baseline GGT two-to-three times the upper limit of normal, 83 subjects had a baseline GGT three-to-five times the upper limit of normal, 59 subjects had a baseline GGT five-to-ten times the upper limit of normal, and 27 subjects had a baseline GGT greater than ten times the upper limit of normal. These GGT values in conjunction with the self-reported screening measures for alcoholism support that the subjects who participated in this study were alcohol abusers.

An elevated AST/ALT ratio of 2 to 3 has also been used as an indicator of chronic alcohol abuse and as an indicator of alcoholic liver disease [102,100]. As shown in Table 7-9, 91 subjects (57 APAP, 34 placebo) had an AST/ALT ratio of greater than 2.0 at baseline. Over 10% of the participants across four studies showed evidence of alcoholic liver disease.

All of the prospective studies also assessed the duration, quantity, and frequency of alcohol use prior to entering the detoxification facility. In order to be enrolled in the Four-Day study, [86] subjects had to report drinking more than six alcoholic drinks daily for at least six weeks. Subjects who participated in the Two-, Three-, and Five-Day studies completed an alcohol history that included questions addressing how much subjects drank each day, how long they had recently been drinking, and how long they had been alcoholics. As shown in Table 7-10, over 50% of the subjects who participated in the studies at RMPDC had been alcoholics for more than 15 years.

Subjects who participated in the Two-, Three-, and Five-Day studies were also asked to indicate the duration of their most recent drinking binge (The question was "Most recently, how long have you been drinking?"). As shown in Table 7-11, the duration of the most recent drinking binge was one-to-four weeks in 27% to 34% of subjects and greater than one month in approximately one-half of the subjects. Inclusion criteria for the Five-Day study required subjects' most recent drinking binge to have included all 7 days prior to study enrollment.

In all subjects who participated in the Two-, Three-, and Five-Day studies, breath alcohol levels were determined at baseline (Table 7-12). In the Two-Day study, breath alcohol levels were detectable at presentation in 81.4% of the subjects in the acetaminophen group and 76.8% of the subjects in the placebo group. In the Three- and Five-Day studies, one of the inclusion criteria was a detectable breathed alcohol level at presentation to facility. Therefore, 100% of the subjects participating in these studies had a detectable breath alcohol level at presentation. In the Two-Day study, the mean breath alcohol level at presentation was 186 mg/dL in subjects in the acetaminophen group and 157 mg/dL in subjects in the placebo group. In the Three- and Five-Day studies the mean breath alcohol level at presentation ranged from 157 to 196 mg/dL.

7.8.3.3.3 Characterization of Alcohol Detoxification in Study Population

In their review of both Two-Day studies, FDA states that alcoholic detoxification history was not reported. The following provides information regarding the alcohol detoxification history from the Two-Day studies, as well as the Three- and Five-Day studies. All studies were conducted at detoxification centers. Alcohol withdrawal severity varies greatly among patients. While patients with mild symptoms may require only supportive nonpharmacological therapy, patients with more severe symptoms may require pharmacological management of alcohol withdrawal [103]. If pharmacological management

is required, benzodiazepines are often considered a first-line treatment [103,104]. In the Three-Day study 31% of subjects were treated with benzodiazepines and in the Five-Day study 23% of subjects were treated with benzodiazepines Table 7-13. These figures are consistent with other published literature with respect to the percentage of alcoholics who require or would be expected to require benzodiazepines for the treatment of alcohol withdrawal [104,105].

7.8.3.3.4 Characterization of Nutritional Status in Study Population

Nutritional deficiencies are common among chronic alcoholics [106]. In all studies coordinated by RMPDC, baseline nutritional status was evaluated. Parameters used to assess nutritional status included clinical examination, body mass index (BMI), and albumin levels.

Clinical examination is a validated approach to nutritional assessment that is at least as accurate as laboratory measurements for assessing nutritional status [107]. As shown in Table 7-14, approximately 19% to 44% of subjects enrolled in the Two-, Three-, and Five-Day studies had mild malnutrition as assessed clinically. Only a few subjects had severe malnutrition. Based on experimental animal data and limited retrospective data, malnutrition has been hypothesized as a potential risk factor for acetaminophen-induced hepatotoxicity, although this theory has not been proven. When the subset of subjects with clinical malnutrition were compared to the subjects without clinical malnutrition, there was no significant difference in ALT measures at any time during the Two-, Three- or Five-Day trials. As shown in Table 7-15 and Table 7-16

The studies coordinated by RMPDC also evaluated nutritional status by calculating BMI. Different references use different BMI values as cutoffs, some varying by gender, for defining different nutritional conditions and what is or is not considered a “low BMI” [108,109,110]. Some recommend referral to a healthcare professional if the BMI is < 22 [111]. In the RMPDC coordinated studies, a BMI of <22 kg/m^2 in men and <21 kg/m^2 in women was considered to be consistent with clinical malnutrition. As shown in Table 7-17, the RMPDC coordinated studies, the mean BMI was 23.4 to 25 kg/m^2 and 17.6% to 33.3% of the subjects enrolled had a BMI consistent with clinical malnutrition.

Serum albumin levels have been used to evaluate nutritional status [112] and hepatic function [113]. Although some malnourished patients and some patients with liver disease have decreased albumin levels, many other factors can affect albumin levels [111]. As

shown in Table 7-4, in the Three-Day and Five-Day studies, the average albumin was 3.9 to 4.2 g/dL.

7.8.3.3.5 Other Baseline Laboratory Values in Study population

In subjects who participated in the studies coordinated by RMPDC, baseline clinical chemistry and hematology laboratory values were assessed. The results of these assessments are listed in Table 7-18 and Table 7-19.

7.8.3.3.6 Use of CYP2E1 Inducing or Inhibiting Drugs in Study Population

Within the proposed rule FDA alludes to individuals who may have enhanced activity of CYP2E1 ("alcoholics and people using anticonvulsants") [71 FR 77337] The most current data reveal that anticonvulsants, such as phenytoin and phenobarbital, are not inducers of CYP2E1 [114] [115]. Isoniazid can induce CYP2E1 [116] and disulfiram can inhibit the activity of CYP2E1 [117,118]. No subjects enrolled in the studies coordinated by RMPDC were receiving isoniazid or disulfiram.

7.8.3.4 Power Calculations

All of the prospective studies were specifically designed to detect small differences in AST and ALT between the acetaminophen and placebo groups. The Pilot Two-Day study had 80% probability for detecting at least a 20 IU/L difference in the AST and ALT means of the two groups [1]. The larger Two-Day study had a power of 95% to detect a mean difference in the AST level of 13.9 IU/L, in the ALT level of 16.6 IU/L, and in the INR of 0.05 [2]. The Three-Day study had a power of 95% to detect mean difference in the serum ALT of 15 IU/L [84]. The Five-Day study had a power of 80% to detect a mean difference in the serum ALT of 17 IU/L [119]. The study by Bartels et al [86] was designed to detect a 0.9 µg/L increase in alpha- glutatione-S-transferase with 80% power.

7.8.3.5 Study Results

7.8.3.5.1 Demographics

Most of the subjects enrolled in all of the studies were males, Table 7-20. Subjects ranged in age from 18 years to 72 years. In all of the studies, there were no significant differences in demographic characteristics between the acetaminophen and placebo groups.

7.8.3.5.2 Hepatic Transaminase Activity

In the Pilot Two-, Two-, Three- and Five-Day studies, there were no statistically significant differences between the acetaminophen and placebo groups for mean changes from baseline in AST, ALT, or INR. There were no reports of liver injury, hepatic dysfunction, or hepatic failure among the over 400 newly abstinent alcoholics who were administered maximum recommended therapeutic doses of acetaminophen for up to five consecutive days.

There was no statistical difference between the 11 (2.1%) subjects treated with acetaminophen and the 4 (1.2%) subjects treated with placebo who developed an ALT > 200 IU/L (p=0.459). In the limited data presented in the abstract by Bartel [86], there was no statistically significant difference between groups in levels of alpha- glutatione-S-transferase, AST, ALT, INR, or in doubling of aminotransferases to 120 IU/L.

As shown in Table 7-21, Table 7-22, and Table 7-23 in all of the studies coordinated by RMPDC, there were no clinically relevant differences between the acetaminophen and placebo groups for mean changes from baseline for AST, ALT or INR respectively.

7.8.3.5.3 Subgroup Analyses

Several post-hoc analyses were performed. Subgroups analyzed included the following: (1) subjects with an AST/ALT ratio of greater than 2.0, (2) subjects with an elevated baseline ALT, (3) subjects positive for hepatitis C virus antibody, (4) subjects with evidence of clinical malnutrition, and (5) subjects who received CYP2E1 substrates, inducers, or inhibitors. As described in detail below, none of these subgroups responded differently to either acetaminophen, and therefore, were determined not to be at risk for hepatotoxicity.

7.8.3.5.3.1 Baseline AST/ALT >2.0

A subgroup analysis was completed on data from all of the studies RMPDC coordinated examining AST/ALT ratios in subjects with a case definition of alcoholic liver disease based on a baseline AST/ALT ratio of >2.0. The results are listed in Table 7-24.

Further analysis of data from the Three-Day study, which had the largest number of subjects meeting the case definition for alcoholic liver disease, demonstrated that among those with an AST/ALT >2.0, there was no statistically significant difference between the acetaminophen and placebo groups for mean ALT. In those with a baseline AST/ALT ratio

of at least 2.0, the peak ALT during the study was 75 IU/L (compared with 312 IU/L for the entire study sample) and no subject developed an ALT that was more than three times the upper limit of normal or experienced an adverse event. Throughout the study, the mean ALT was significantly higher in the group without evidence of alcoholic liver disease by AST/ALT ratio than in the group with evidence of alcoholic liver disease.

7.8.3.5.3.2 Elevated Baseline ALT

In the Three-Day study there were 135 subjects (92 subjects in the acetaminophen group and 43 in the placebo group) with a serum ALT greater than the upper limit of normal at baseline. The ALT groups means of these subjects were consistently two-to-three times higher than those observed in subjects without an elevated baseline ALT but there were no statistically significant differences between groups.

The Five-Day study [85] included 37 subjects (17 subjects in the acetaminophen group and 20 in the placebo group) who had a baseline ALT of >40 IU/L. Among subjects with elevated baseline ALT, there were no significant differences between treatment groups for changes in ALT, AST, and INR.

7.8.3.5.3.3 Subjects Positive for Hepatitis C Virus Antibody

The Five-Day study [85] included 41 subjects (18 subjects in the acetaminophen group and 23 in the placebo group) who were positive for hepatitis C virus (HCV) antibody. As expected, ALT levels were higher in subjects who were positive for HCV than in those who were HCV-negative. However, when only HCV-positive subjects were examined, there were no significant differences between the acetaminophen and placebo groups for changes in ALT, AST, and INR.

7.8.3.5.3.4 Malnutrition

A post hoc, subgroup analysis of subjects in the Two-Day study who had a low BMI or clinical malnutrition demonstrated no evidence of an increase in hepatic enzyme levels [2]. An analysis of data from the Two- and Three-Day studies demonstrated that neither BMI nor any degree of malnutrition correlated with increases in ALT [84].

7.8.3.5.3.5 Glutathione

McNeil disagrees with FDA's contention in the proposed rule that "… more specific hepatic evaluations such as …glutathione levels… would have enabled a better evaluation of

chronic alcohol use and underlying alcohol induced liver abnormalities." There are no data to support that glutathione concentrations offer a better evaluation of chronic alcohol use and underlying alcohol-induced liver abnormalities than the extensive history and laboratory evaluations performed in the studies coordinated by RMPDC.

Plasma glutathione concentrations were measured in the Three-Day study in a subset of 79 subjects (56 randomized to acetaminophen and 23 randomized to placebo) at baseline and Day 3 [84]. At baseline, plasma glutathione concentrations in both the acetaminophen (2.17±0.97 μM) and placebo (1.90±0.68 μM) groups were lower than normal, and no differences were detected between the group means. Plasma glutathione levels were measured at different times with respect to the dosing of acetaminophen on Day 3: 26-27% of samples were taken prior to the first dose of the day, 60-61% of samples were obtained within 2 hours after the first dose of the day and 12-13% were taken between 2-4 hours after the first dose. After treatment, mean plasma glutathione concentrations increased to 2.27±0.85 μM in the acetaminophen group and to 2.02±0.74 μM in the placebo group, a difference that was not statistically significant. No significant correlation was observed during the course of the study between plasma glutathione levels and changes in ALT, AST, or INR ($p>0.05$). The increase in glutathione, in both the acetaminophen and placebo groups, that was observed in the Three-Day study is probably a result of termination of alcohol ingestion.

In the proposed rule, "FDA also finds that a 2-day treatment period may be too short to deplete the lowered hepatic glutathione capacity in alcoholic people." The underlying supposition of this statement is incorrect in that it assumes less-than-normal plasma concentrations of reduced glutathione indicate a lowered hepatic glutathione capacity in alcoholic people to metabolize therapeutic doses of acetaminophen. There are no available scientific data in alcoholic subjects showing that hepatic glutathione can be depleted with therapeutic dosing, as true depletion is defined as an intracellular concentration below 10% of normal [3].

In contrast, prospective data in chronic alcoholics given a 2-g acetaminophen dose on the second day of abstinence, show the rates of glutathione consumption and repletion with acetaminophen metabolism were similar to control subjects even though baseline plasma glutathione concentrations were lower for the chronic alcoholic subjects [4]. In both groups, plasma glutathione concentrations reached a minimum at three hours after the dose and returned to baseline at the same time, and the amounts of glutathione consumed were nearly identical. These data in chronic alcoholics provide evidence that hepatic glutathione

concentrations, reflected by surrogate plasma concentrations, were adequate to metabolize a supratherapeutic acetaminophen dose despite lower baseline values.

The plasma glutathione data from the Three-Day study in a larger number of chronic alcoholics are consistent with this published report in that they clearly show steady-state plasma glutathione concentrations did not change after administration of maximum-labeled daily doses of acetaminophen for three consecutive days (totaling 12 g) compared with placebo.

7.8.3.5.3.6 Renal Function

In all of the RMPDC coordinated studies, renal function was assessed by monitoring BUN and creatinine periodically throughout the study. There were no clinically relevant differences between the acetaminophen and placebo groups for mean changes from baseline in BUN or creatinine.

7.8.3.6 Study Conclusions

The maximum daily therapeutic dose of acetaminophen, 4 g/day, administered to newly abstinent chronic alcoholics did not result in hepatotoxicity, hepatic dysfunction, or hepatic failure. Alcoholics can safely take the maximum labeled daily dose of acetaminophen (4 g/day).

7.8.4 Discussion

Five double-blind, randomized, placebo-controlled studies evaluated hepatic function following administration of therapeutic doses of acetaminophen to newly abstinent alcoholic subjects, who would have been at maximum hypothetical risk of acetaminophen-induced hepatotoxicity. FDA has not considered most of these data in its justification for its proposed amendments to the TFM for OTC IAAA drug products.

Hypothetically, if there were a potential risk of hepatic injury following therapeutic doses of acetaminophen, newly abstinent alcoholics would be the “subpopulation” of chronic alcoholics at greatest risk within the first two days of ceasing alcohol consumption. During this short period, CYP2E1 is maximally induced, alcohol is not present to inhibit CYP2E1, and glutathione concentrations may be diminished. Since multiple double-blind, randomized, placebo-controlled studies conducted by different investigators at multiple detoxification sites in both the US and Canada have shown that the “subpopulation” with the greatest hypothetical risk can safely take the maximum-labeled therapeutic doses of

acetaminophen for multiple days, there is no reason to believe that any other "subpopulation" would be at any greater risk.

In all studies, there were no significant differences in mean AST, ALT, or INR values between the acetaminophen and placebo groups following dosing with the current maximum-labeled daily dose of acetaminophen (4 g/day). In addition, one study showed that continuous dosing of acetaminophen had no effect on plasma glutathione concentrations and another found no significant effect on alpha glutathione S-transferase levels. Furthermore, there was no significant difference between groups in the number of subjects who developed an AST or ALT >200IU/L. Multiple *post hoc* evaluations, including those of subjects with baseline elevations in ALT levels or AST/ALT ratios, those of subjects who were positive for hepatitis C antibody, and those of subjects who were malnourished, demonstrated no statistically significant differences between the acetaminophen and placebo groups in mean values for AST, ALT, or INR.

If the chronic alcoholics enrolled in these studies did not develop hepatic damage when they were administered acetaminophen while not actively drinking, then it is unlikely that they would develop hepatic damage if they were administered acetaminophen while actively drinking. Most authorities of alcohol-acetaminophen science and the published data indicate that actively drinking chronic alcoholics may be protected against acetaminophen-associated hepatic injury.

The safety results were replicated across multiple double-blind, randomized, placebo-controlled studies conducted by different investigators at multiple detoxification sites in both the US and Canada. Importantly, these safety results are not surprising, because they are consistent with the clinical acetaminophen metabolism data from several studies that compared the biotransformation of acetaminophen between nondrinking control subjects and chronic alcoholics after ceasing alcohol consumption. Overall, the metabolism data show that there are no, or only fairly small, changes in thiols produced within the first few days after ceasing alcohol consumption, confirming that the effect of alcohol on acetaminophen oxidation by CYP2E1 induction is moderate at best. Therefore, the metabolic rationale for hypothesizing increased risk of acetaminophen-induced hepatotoxicity at therapeutic doses in chronic alcoholics is not substantiated by scientific data. As born out by the clinical safety data from the prospective, randomized studies, people who consume alcohol, even the hypothetically most vulnerable subpopulation of alcohol users, can safely use maximum-labeled daily doses of acetaminophen.

7.8.5 New Clinical Safety Data from a Prospective, Double-Blind, Placebo Controlled Study of Maximum Therapeutic Doses of Acetaminophen (4 g/d) for Consecutive 10 Days in Adults with an Average Alcohol Consumption Between One to Three Drinks per Day

McNeil is aware of one randomized, double-blind, placebo-controlled study in which maximum-labeled daily doses of acetaminophen, 4 g/day, were administered for ten days to adults with an average alcohol consumption between one to three alcoholic drinks/day [120]. No subject developed hepatotoxicity, hepatic dysfunction, or hepatic failure. No subject developed symptoms of hepatic injury.

7.8.5.1 Study Objectives

The primary objective was to determine the effect of ten days of the maximum therapeutic dose of acetaminophen on serum ALT activity in adults with average alcohol consumption between one and three drinks per day [120].

7.8.5.2 Study Design

This was a randomized, double-blind, placebo-controlled trial. The randomization of acetaminophen to placebo was 2:1. Subjects randomized to acetaminophen were instructed to take 1g of acetaminophen four times daily, at least four hours apart, for 10 days. They also were instructed to avoid taking other acetaminophen-containing medications and to continue their normal drinking pattern.

Subjects were provided with a logbook to note the time of each treatment dose. Subjects were also asked to record the number and type of alcoholic drinks consumed during the study and daily average ethanol consumption was calculated by determining the total number of drinks (defined as 12 ounces of beer, 4 ounces of wine, or 1 ounce of liquor) consumed each week and dividing by seven.

Laboratory evaluation included a hepatic panel (ie, ALT, AST, alkaline phosphatase, bilirubin, and total protein) performed at baseline, on Day 4 of study treatment, and on Day 11, one day after completion of the treatment period. Subjects were asked to report any adverse events on Days 2, 4, 6, 8, and 11.

The primary outcome was the mean change in AST from baseline to Days 4 and 11. Secondary outcomes were change in mean ALT, alkaline phosphatase, bilirubin, and total protein from baseline to Days 4 and 11, the number of subjects who had an increase in

serum ALT or alkaline phosphatase of three times the upper limit of the reference range along with an increase in serum bilirubin to 1.5 times the upper limit of the reference range, and the number of subjects that developed hepatotoxicity, defined as a serum ALT or AST >1000 IU/L [40].

7.8.5.3 Study Population

This study enrolled healthy volunteers with a history of "moderate" alcohol consumption for the preceding two months (defined as an average daily ethanol consumption between one and three drinks) and at least one alcoholic beverage in the 48 hours prior to enrolling. Subjects were excluded if they admitted to being an alcoholic, had average baseline consumption of more than three alcoholic drinks per day, ingested more than four grams of acetaminophen per day for any of the four days preceding study enrollment, had a baseline serum acetaminophen level of >132 µmol/L, (20 mcg/mL), had baseline serum AST or ALT levels greater than 50 IU/L, or were pregnant. Other exclusion criteria included clinical intoxication, psychiatric impairment, or inability to give informed consent, a known hypersensitivity to acetaminophen, and enrollment in another trial currently or in the preceding three months.

7.8.5.4 Power Calculations

The sample size of 50 controls and 100 acetaminophen-treated subjects was determined to provide 80% power to detect a 24 IU/L difference in mean serum ALT between groups.

7.8.5.5 Statistical Analysis

Two-way repeated measures analysis of variance was used to compare laboratory measurements between treatment groups and Fischer's Exact Test was used to compare the proportion of subjects that met criteria for drug induced liver injury and hepatotoxicity between treatment groups. The change in ALT was correlated with the total number of drinks consumed during the ten-day treatment period using a Pearson Correlation Coefficient.

7.8.5.6 Rechallange Phase

After the initial trial was complete, any subjects who experienced an elevation of their serum ALT or AST above the upper limits of the reference range any time during the initial study were asked if they wanted to participate in the rechallenge phase. Inclusion and exclusion criteria for this phase were the same as in the initial phase except that ethanol consumption from zero-to-three drinks per day was allowed due to changes in the subjects'

drinking habits. During this rechallenge phase, subjects received the same treatment they were administered during the initial phase and blood samples were collected at Days 4, 7, 9, and 11.

7.8.5.6.1 Results

7.8.5.6.1.1 Demographic and Baseline Characteristics

A total of 173 subjects were recruited, 156 received one dose of study medication, and 150 completed the study. The two groups had similar demographic and baseline characteristics (Table 7-25). The average age of the subjects in the control group was 34 years and the average age of subjects in the acetaminophen group was 32.6 years. The majority of subjects were non-Hispanic white.

Compliance with the study treatment was similar between groups. Subjects in both groups drank an average of two drinks per day during the study. At baseline, one subject in the acetaminophen group was positive for hepatitis B antigen and another was positive for hepatitis C antibody.

7.8.5.6.1.2 Hepatic Testing

7.8.5.6.1.2.1 Initial Study

No subject in either group developed hepatotoxicity, hepatic dysfunction, or hepatic failure. Mean ALT, AST, total bilirubin, alkaline phosphatase, and total protein for both groups are presented in Table 7-26. Mean changes from baseline for these tests are provided in Table 7-27. While there was no change from baseline in serum ALT in either group at Day 4 or in the placebo group at Day 11, the acetaminophen group had a statistically significant 8.7 IU/L increase in mean ALT at Day 11. The acetaminophen and placebo groups did not have significant changes from baseline in AST at Day 4 or Day 11. Neither the acetaminophen nor the placebo group had significant changes from baseline in serum bilirubin at Day 4 or 11. None of the subjects met criteria for Hy's Law. This finding is consistent with previous findings in some non-drinking adults [121,122].

7.8.5.6.1.2.2 Rechallenge Study

Ten (37%) of the twenty-seven subjects eligible for enrollment in the rechallenge phase participated. Among the nine acetaminophen treated subjects, the mean increases from baseline in ALT were 2.8 IU/L, 10.3 IU/L, 19.1 IU/L, and 16.8 IU/L on Days 4, 7, 9, and 11, respectively. Compared with baseline, there was an increase in ALT at Day 11 for all

subjects. In seven (77.7%) of these subjects, the increase in ALT at Day 11 was smaller during the rechallenge phase than in the initial study. During the rechallenge phase no subject developed hepatotoxicity, hepatic dysfunction, or hepatic failure.

7.9 Study Conclusions

The maximum labeled daily therapeutic dose of acetaminophen, 4 g/day, for ten consecutive days did not result in hepatotoxicity, hepatic dysfunction, or hepatic failure in actively drinking adults with average alcohol consumption between one and three drinks per day. Recommended doses of acetaminophen do not result in hepatotoxicity in occasional regular drinkers. This study supports the safety of recommended doses of acetaminophen in occasional regular users of alcohol.

Table 7-1. Studies Examining Hepatic Function Following Administration of Therapeutic Doses of Acetaminophen to Newly Abstinent Chronic Alcoholics

Study [Reference]	Study Design	Treatment	N	Study Results
Pilot Two-Day [1]	R, DB, PC, SC	APAP 1 g q4h (4g/d) for 2 days Placebo Initiated immediately after cessation of alcohol.	30 30	**Study Population:** Alcoholic subjects entering a detoxification facility with a baseline AST and ALT ≤120 U/L and INR ≤1.5. **Outcome measures:** ALT, AST, and INR were performed at baseline and repeated on Day 4. AST and INR were also performed on Day 2. **Results:** There were no statistically significant differences between groups in mean AST, ALT, or INR levels at any time. There were no statistically significant differences between groups with respect to frequency of AST, ALT, INR, BUN, or creatinine elevations.
Two-Day [2]	R, DB, PC, SC	APAP 1 g q4h (4g/d) for 2 days Placebo Treatment initiated immediately after cessation of alcohol.	102 99	**Study Population:** Alcoholic subjects entering a detoxification facility with a baseline AST and ALT ≤120 U/L and INR ≤1.5. **Outcome measures:** ALT, AST, and INR were performed at baseline and repeated on Days 2 and 4. **Results:** No statistically significant differences between groups in AST, ALT, or INR levels after drug dosing. Number of subjects who developed an AST level above baseline: APAP-41 and placebo-42 (p=0.77). Number of subjects who developed an ALT level above baseline: APAP-52 and placebo-62 (p=0.12). Number of subjects who developed an INR level above baseline: APAP-52 and placebo-53 (p=0.78). Four subjects in the APAP group and 5 in the placebo group developed an AST or ALT level >120 U/L. No subject in either group developed an AST or ALT level >200 U/L. Mean AST level on Day 2: APAP-33.3 U/L and placebo 38.0 U/L. Mean ALT level on Day 2: APAP-33.1 U/L and placebo-37.3 U/L. Mean INR on Day 2: APAP-0.95 and placebo-0.95. Mean AST level on Day 4: APAP-38.0 U/L and placebo 37.5 U/L. Mean ALT level on Day 4: APAP-40.1 U/L and placebo-41.9 U/L. Mean INR on Day 4: APAP-0.96 and placebo-0.98. Post-hoc analysis found no increase in enzyme levels among subjects with a low body mass index or those judged as malnourished.

Table 7-1. Studies Examining Hepatic Function Following Administration of Therapeutic Doses of Acetaminophen to Newly Abstinent Chronic Alcoholics

Study [Reference]	Study Design	Treatment	N	Study Results
Three-Day [84]	R, DB, PC, MC	APAP 1 g q4h (4g/d) for 3 days Placebo Treatment initiated immediately following cessation of alcohol intake.	258 114	**Study Population:** Alcoholic subjects entering a detoxification facility with a baseline AST and ALT ≤200 U/L and INR ≤1.5. **Outcome measures:** ALT, AST, INR, and bilirubin were measured at baseline and repeated on days 2 to 5. In a subset of subjects plasma glutathione levels were measured at baseline and on day 3. **Results:** There were no statistically significant differences between groups in mean ALT or AST levels at baseline or at any time after drug administration. The peak mean ALT was 57 IU/L with APAP and 55 IU/L with placebo. Mean serum ALT on day 2: APAP-45 and placebo-46 (p=-0.949). Mean serum ALT on day 3: APAP-45 and placebo-50 (p=-0.245). Mean serum ALT on day 4: APAP-48 and placebo-52 (p=-0.411). Mean serum ALT on day 5: APAP-57 and placebo-55 (p=-0.706). ALT stayed the same or decreased in 32% of APAP and 28% of placebo subjects. Number of subjects who developed an ALT level greater than 3 times normal: APAP-19 and placebo-8. Number of subjects who developed an ALT >200 IU/L: APAP-8 and placebo-2. There was no significant change in mean INR or total bilirubin between the study groups throughout the study (p>0.05). In the subset of subjects in whom plasma glutathione levels were measured, there were no significant differences between groups; glutathione levels increased in both groups. In subjects with a baseline AST/ALT ratio ≥2, subjects who presented with an elevated ALT, and subjects attaining a peak ALT greater than 200 IU/L there were no significant differences between groups in mean ALT. Neither body mass index nor any degree of malnutrition correlated with increases in ALT.

Table 7-1. Studies Examining Hepatic Function Following Administration of Therapeutic Doses of Acetaminophen to Newly Abstinent Chronic Alcoholics

Study [Reference]	Study Design	Treatment	N	Study Results
Five-Day [85]	R, DB, PC, MC	APAP 1 g q4h (4g/d) for 5 days Placebo Initiated immediately following cessation of alcohol.	74 68	**Study Population:** Alcoholic patients entering a detoxification facility with a baseline AST and ALT ≤200 U/L and INR ≤1.5. **Outcome measures:** ALT, AST, and INR were performed at baseline and repeated on days 2, 4, 6, and 7. **Results:** There were no statistically significant differences between groups for change in AST, ALT, or INR after drug dosing, even in the presence of elevated baseline ALT (>40 IU/L) or in patients reactive for hepatitis C antibody.
Four-Day [86]	R, TB, PC, SC	APAP Sustained release 1.3 g q8h x 11 doses Placebo Initiated within 12 to 27 hours following cessation of alcohol.	40	**Study Population:** Chronic alcohol abusers who had discontinued alcohol consumption 12-72 hours prior to enrollment and had a baseline AST and ALT ≤120 U/L and INR ≤1.5. **Outcome measures:** ALT, AST, INR, and α-GST were performed at baseline and repeated daily for 5 days. **Results:** There were no statistically significant differences between groups in α-GST, AST, ALT, or INR after drug dosing. Relative change in α-GST was 46% vs 29% (p=0.5). Relative change in AST was –3% vs. –6% (p=0.8)..

Abbreviations: α-GST= α-gluathione-*S*-transferase, APAP=acetaminophen, DB=double-blind, PC=placebo controlled, MC=multi-center, R=randomized, SC=single-center, TB=triple blind.

Table 7-2. Summary of Study Designs

	Pilot Two-Day [1]	Two-Day [2]	Three-Day [84]	Five-Day [85]	Four-Day [86]
Study Design	R, DB, PC, SC	R, DB, PC, SC	R, DB, PC, MC	R, DB, PC, MC	R, TB, PC, SC
Randomization (acetaminophen:placebo)	1:1	1:1	2:1	1:1	1:1
Total number of subjects who completed the study	60	201	385	130	40
Acetaminophen Dose	1 g q4h x 4 doses/day	1 g q4h x 4 doses/day	1 g q4h x 4 doses/day	1 g q4h x 4 doses/day	1.3 g q8h
Duration of acetaminophen therapy	2 days	2 days	3 days	5 days	11 doses
Monitoring of AST, ALT, INR	Baseline and day 4, AST and INR also monitored on day 2	Baseline, day 2, day 4	Baseline, days 2, 3, 4, 5	Baseline, days 2, 4, 6 and 7	Baseline, days 2, 3, 4, 5
Additional Monitoring	BUN and creatinine at baseline and on day 4	BUN and creatinine at baseline and on days 2 and 4	BUN and creatinine at baseline and on day 5 Plasma glutathione at baseline and day 3 in subset of subjects	BUN and creatinine at Baseline, days 2, 4, 6, 7. Viral hepatitis screen at baseline.	α-GST at baseline and on days 2, 3, 4, and 5

Table 7-2. Summary of Study Designs

	Pilot Two-Day [1]	Two-Day [2]	Three-Day [84]	Five-Day [85]	Four-Day [86]
Inclusion Criteria	Adult alcoholics who recently entered a detoxification center	Adult alcoholics who recently entered a detoxification center	Adult alcoholics who recently entered a detoxification center and had a detectable breath ethanol concentration at admission	Adult alcoholics who recently entered a detoxification center, had a detectable breath ethanol concentration at admission, been drinking at least 7days prior to enrollment and were given first dose of study medication within 12 hours of estimated sober time	Chronic alcoholics (>6 drinks/day for ≥6 weeks) who discontinued alcohol consumption 12 to 72 h prior to enrollment
Exclusion based on AST, ALT, INR	AST or ALT>120 IU/L or INR>1.5	AST or ALT>120 IU/L or INR>1.5	AST or ALT>200 IU/L or INR>1.5	AST or ALT>200 IU/L or INR>1.5	AST or ALT>120 IU/L or INR>1.5

Table 7-2. Summary of Study Designs

	Pilot Two-Day [1]	Two-Day [2]	Three-Day [84]	Five-Day [85]	Four-Day [86]
Other exclusion criteria	History of ingesting >4 g APAP on any of 4 preceding days Baseline serum APAP>20 µg/mL	History of ingesting >4 g APAP on any of 4 preceding days Baseline serum APAP>20 µg/mL Clinical intoxication at the time first dose of study medication administered Hypersensitivity to APAP Positive pregnancy test at baseline	History of ingesting >4 g APAP on any of 4 preceding days Baseline serum APAP>20 µg/mL Hypersensitivity to APAP Clinical intoxication at the time first dose of study medication administered Hypersensitivity to APAP Clinical intoxication at the time first dose of study medication administered Positive pregnancy test at baseline	History of ingesting >4 g APAP on any of 4 preceding days Baseline serum APAP>20 µg/mL Hypersensitivity to APAP Clinical intoxication at the time first dose of study medication administered Positive pregnancy test at baseline	Self-reported viral hepatitis or intravenous drug use

Abbreviations: α-GST= α-gluathione-*S*-transferase, APAP=acetaminophen, DB=double-blind, PC=placebo controlled, MC=multi-center, R=randomized, SC=single-center, TB=triple blind

Table 7-3. Exclusion at Baseline Based on Elevated Liver Function Tests in Newly Abstinent Chronic Alcoholics Screened for Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Liver Exclusion Criteria	Subjects Screened	Subject Excluded Due to Baseline elevated AST, ALT, or INR; N (%)
Pilot Two-Day [1]	AST >120 IU/L ALT >120 IU/L INR >1.5	74	13 (17.6%)
Two-Day [2]	AST >120 IU/L ALT >120 IU/L INR >1.5	284	30 (10.6%)
Three-Day [84]	AST >200 IU/L ALT >200 IU/L INR >1.5	509	24 (4.7%)
Five-Day [85]	AST >200 IU/L ALT >200 IU/L INR >1.5	181	22 (12.2%)

Abbreviations: APAP-acetaminophen, ALT-alanine aminotransferase, AST-aspartate aminotransferase, INR- international normalized ratio

Table 7-4. Baseline Values (Mean ± SD; Range) Clinical Laboratory Tests in the Acetaminophen Clinical Studies in Alcohol Abusers

Study [Reference]	Treatment	AST (IU/L)	ALT (IU/L)	INR	Alkaline Phosphatase (IU/L)	Total Bilirubin (mg/dL)	Total Protein (g/dL)	Albumin (g/dL)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	50.9 ± 28.3 17-113	34.2 ± 21.2 9-85	1.04 ± 0.16 0.79-1.5	Not Measured	0.8 ± 0.5 0.3-2.5	7.1 ± 0.7 5.7-8.4	Not Measured
	Placebo (n=30)	44.2 ± 26.0 16-111	31.1 ± 18.0 8-93	0.98 ± 0.13 0.73-1.28	Not Measured	1.0 ± 0.6 0.3-2.6	7.5 ± 0.6 6.2-8.6	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	40.0 ± 20.4 14-112	34.6 ± 19.2 9-92	0.96 ± 0.08 0.80-1.18	Not Measured	0.8 ± 0.4 0.2-2.3	7.6 ± 0.5 6.4-8.9	Not Measured
	Placebo (n=99)	41.6 ± 23.5 12-116	36.5 ± 20.2 9-109	0.98 ± 0.08 0.82-1.34	Not Measured	0.7 ± 0.4 0.2-2.5	7.4 ± 0.7 5.5-9.1	Not Measured
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	55.2 ± 38.5 6-198	49.2 ± 38.9 4-189	0.96 ± 0.09 0.79-1.40	96.1 ± 41.8 37-529	0.7 ± 0.5 0.1-4.1	7.2 ± 0.6 5.4-8.8	3.9 ± 0.4 2.8-5.1
	Placebo (n=135)	54.8 ± 38.1 12-194	47.0 ± 36.8 8-175	0.96 ± 0.09 0.80-1.30	96.7 ± 39.8 40-352	0.7 ± 0.5 0.1-2.8	7.4 ± 0.7 5.7-9.6	3.9 ± 0.4 2.1-4.8
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	61.9 ± 45.3 15-194	48.2 ± 36.9 8-178	0.94 ± 0.12 0.79-1.50	101.7 ± 59.7 51-547	0.8 ± 0.7 0.18-4.73	7.5 ± 0.6 6.0-9.1	4.2 ± 0.5 2.0-4.9
	Placebo (n=68)	53.2 ± 34.5 16-195	47.2 ± 32.5 10-159	0.92 ± 0.07 0.77-1.10	97.3 ± 29.3 32-199	0.6 ± 0.3 0.2-1.6	7.3 ± 0.6 5.9-8.7	4.1 ± 0.4 2.2-4.8

Abbreviations: APAP-acetaminophen, ALT-alanine aminotransferase, AST-aspartate aminotransferase, INR- international normalized ratio

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Table 7-5. Baseline Scores on CAGE and the Brief Michigan Alcoholism Screening Test (MAST) for Newly Abstinent Chronic Alcoholics Enrolled in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	CAGE		Brief MAST		DSM-IV[a]	
	≥2 Yes Answers (%)	4 Yes answers (%)	Score ≥6 points (%)	Mean ± SD (range)	Substance/Alcohol Dependence (%)	Substance/Alcohol Abuse (%)
Pilot Two-Day [1]	57 (95.0)	35 (58.3)	Not Measured	Not Measured	Not Measured	Not Measured
Two-Day [2]	189 (94.0)	124 (61.7)	198 (98.5)	23.5 ± 4.7 (0-29)	Not Measured	Not Measured
Three-Day [84]	419 (94.6)	241 (54.4)	436 (98.4)	22.5 ± 6.2 (0-29)	Not Measured	Not Measured
Five-Day [85]	134 (94.4)	82 (57.7)	139 (97.9)	21.7 ± 5.9 (2-29)	138 (97.2)	3 (2.1)

[a]Subjects were first evaluated for substance dependence. If a subject did not meet the criteria for substance dependence (n=4) their drinking behavior was evaluated for substance abuse.

Table 7-6. Self-Reporting of Alcoholism in Newly abstinent Chronic Alcoholics Enrolled in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Number of Self-Reported Alcoholics n (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured
	Placebo (n=30)	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	99 (97.1)
	Placebo (n=99)	99 (100.0)
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	301 (97.7)
	Placebo (n=135)	133 (98.5)
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	69 (93.2)
	Placebo (n=68)	67 (98.5)

Abbreviations: APAP-acetaminophen

Table 7-7. Baseline Values (Mean ± SD; Range) for GGT in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Baseline GGT (IU/L)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured
	Placebo (n=30)	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	124.6 ± 205.4 14-1672
	Placebo (n=99)	128.9 ± 282.1 1-1922
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	161.2 ± 308.2 9-3492
	Placebo (n=135)	167.7 ± 274.5 12-1893
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	179.6 ± 251.2 15-1345
	Placebo (n=68)	91.3 ± 79.1 18-345

Abbreviations: APAP-acetaminophen, GGT- Gamma Glutamyl Transferase

Table 7-8. Baseline Gamma Glutamyl Transferase (GGT) by Multiples of Upper Limit of Normal in Acetaminophen Prospective, Randomized Clinical Studies, Intent-to-Treat Population

Study [Reference]	Treatment	Baseline GGT/upper limit of normal (No.(%))						
		≤1xULN	>1 through 1.5xULN	>1.5 through 2xULN	>2 through 3xULN	>3 through 5xULN	>5 through 10xULN	>10xULN
Pilot Two-Day[a] [1]	APAP 4 g/d x 2 days (n=30)	Not Measured						
	Placebo (n=30)	Not Measured						
Two-Day[a] [2]	APAP 4 g/d x 2 days (n=102)	42 (42.9)	14 (14.3)	13 (13.3)	9 (9.2)	9 (9.2)	9 (9.2)	2 (2.0)
	Placebo (n=99)	45 (46.9)	15 (15.6)	9 (9.4)	7 (7.3)	9 (9.4)	7 (7.3)	4 (4.2)
Three-Day [a,b] [84]	APAP 4 g/d x 3 days (n=308)	153 (50.3)	30 (9.9)	25 (8.2)	35 (11.5)	28 (9.2)	23 (7.6)	10 (3.3)
	Placebo (n=135)	66 (49.6)	18 (13.5)	6 (4.5)	14 (10.5)	15 (11.3)	7 (5.3)	7 (5.3)
Five-Day[a,c] [85]	APAP 4 g/d x 5 days (n=74)	26 (35.1)	10 (13.5)	4 (5.4)	7 (9.5)	13 (17.6)	9 (12.2)	4 (5.4)
	Placebo (n=68)	31 (45.6)	14 (20.6)	6 (8.8)	6 (8.8)	7 (10.3)	4 (5.9)	0 (0)

Abbreviations: APAP-acetaminophen, GGT- Gamma Glutamyl Transferase, ULN-upper limit of normal ,ULN of GGT: [a]CARES site 50 IU/L male, 40 IU/L female; [b]RCKC site Lab1 105 IU/L male, 98 IU/L female; [b]RCKC site Lab2 80 IU/L male, 60 IU/L female; [c]CAMH site Lab1 85 IU/L male, 55 IU/L female; [c]CAMH site Lab2 59 IU/L male and female.

Table 7-9. Number of Subjects in Acetaminophen Prospective, Randomized Clinical Studies with an Elevated AST/ALT ratio

Study [Reference]	Treatment	Subjects with a AST/ALT Ratio Greater Than 2.0 {No(%)}
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	10 (33.3)
	Placebo (n=30)	6 (20)
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	5 (4.9)
	Placebo (n=99)	8 (8.1)
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	30 (9.7)
	Placebo (n=135)	16 (11.9)
Five-Day [85]	APAP 4 g/d x 5d (n=74)	12 (16.2)
	Placebo (n=68)	4 (5.9)

Table 7-10. Number (%) of Newly Abstinent Chronic Alcoholics By Duration of Alcoholism Enrolled in the Acetaminophen Prospective Clinical Studies

Study [Reference]	Treatment	Alcoholic for 0-5 years (%)	Alcoholic for 6-10 years (%)	Alcoholic for 11-15 years (%)	Alcoholic for 16-20 years (%)	Alcoholic for >20 years (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured				
	Placebo (n=30)	Not Measured				
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	Overall: over 45% reported being an alcoholic for >20 years				
	Placebo (n=99)					
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	22 (7.1)	46 (14.9)	37 (12.0)	61 (19.8)	132 (42.9)
	Placebo (n=135)	5 (3.7)	11 (8.1)	17 (12.6)	26 (19.3)	72 (53.3)
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	6 (8.1)	14 (18.9)	11 (14.9)	16 (21.6)	22 (29.7)
	Placebo (n=68)	8 (11.8)	12 (17.6)	6 (8.8)	7 (10.3)	34 (50.0)

Table 7-11. Duration of Most Recent Drinking Binge in Newly abstinent Chronic Alcoholics Enrolled in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Duration of Most Recent Drinking Binge <1 week (%)	Duration of Most Recent Drinking Binge 1–4 weeks (%)	Duration of Most Recent Drinking Binge >1-6 months (%)	Duration of Most Recent Drinking Binge >6 months (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured			
	Placebo (n=30)	Not Measured			
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	24 (23.5)	34 (33.3)	17 (16.7)	25 (24.5)
	Placebo (n=99)	24 (24.2)	27 (27.3)	20 (20.2)	24 (24.2)
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	56 (18.2)	98 (31.8)	79 (25.6)	75 (24.4)
	Placebo (n=135)	22 (16.3)	36 (26.7)	31 (23.0)	45 (33.3)
Five-Day[a] [85]	APAP 4 g/d x 5 days (n=74)	0 (0)	24 (32.4)	22 (29.7)	27 (36.5)
	Placebo (n=68)	0 (0)	23 (33.8)	18 (26.5)	27 (39.7)

Abbreviations: APAP-acetaminophen
Binge: a period of time during which you have had at least one alcoholic beverage every day
[a]The inclusion criteria for the Five-Day dosing study required participants to have been drinking for at least seven days prior to study enrollment.

Table 7-12. Alcohol Level at Presentation in Newly abstinent Chronic Alcoholics Enrolled in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Subjects with Detectable Breath Alcohol Level at Presentation n (%)	Breath Alcohol at Presentation mg/dL mean ± SD range
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured	
	Placebo (n=30)	Not Measured	
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	83 (81.4)	186.4 ± 109.2 0-447
	Placebo (n=99)	76 (76.8)	157.0 ± 101.0 0-370
Three-Day[a] [84]	APAP 4 g/d x 3 days (n=308)	308 (100.0)	157 ± 99 1-550
	Placebo (n=135)	135 (100.0)	161 ± 93 1-710
Five-Day[a] [85]	APAP 4 g/d x 5 days (n=74)	74 (100.00)	188 ± 82 3-454
	Placebo (n=68)	68 (100.00)	196 ± 90 5-484

Abbreviations: APAP-acetaminophen
[a] The inclusion criteria for the Three-Day and Five- Day Dosing Studies required participants to have a detectable breathed alcohol level at presentation to facility.

Table 7-13. Use of Benzodiazepines in Newly abstinent Chronic Alcoholics in Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Subjects Treated with Benzodiazepines, n (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured
	Placebo (n=30)	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	Not Measured
	Placebo (n=99)	Not Measured
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	90 (29.2)
	Placebo (n=135)	48 (35.6)
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	23 (31.1)
	Placebo (n=68)	10 (14.7)

Abbreviations: APAP-acetaminophen

Table 7-14. Clinical Assessment of Nutritional Status at Baseline in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Normal n (%)	Mild Malnutrition n (%)	Severe Malnutrition n (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)		Not Measured	
	Placebo (n=30)		Not Measured	
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	74 (72.5)	26 (25.5)	0 (0)
	Placebo (n=99)	74 (74.7)	19 (19.2)	1 (1.0)
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	167 (54.2)	136 (44.2)	3 (1.0)
	Placebo (n=135)	74 (54.8)	59 (43.7)	1 (0.7)
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	53 (71.6)	21 (28.4)	0 (0)
	Placebo (n=68)	51 (75.0)	16 (23.5)	1 (1.5)

Abbreviations: APAP-acetaminophen

Table 7-15. Comparison of Peak Alanine Aminotransferase Levels by Multiples of Upper Limit of Normal (Mean ± SD; Range) Stratified by Clinical Assessment of Nutritional Status at Baseline

Study [Reference]	Treatment	Normal	Clinical Malnutrition (mild or severe)	p-value
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured		N/A
	Placebo (n=30)	Not Measured		N/A
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	1.13 ± 0.82 0.31 – 4.55	1.10 ± 0.70 0.30 – 3.23	0.845
	Placebo (n=99)	1.10 ± 0.68 0.28 – 3.83	1.14 ± 0.66 0.30 – 2.95	0.834
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	1.41 ± 1.18 0.22 – 7.80	1.38 ± 1.11 0.18 – 6.60	0.799
	Placebo (n=135)	1.24 ± 0.90 0.17 – 4.25	1.41 ± 1.34 0.16 – 7.05	0.359
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	1.58 ± 1.13 0.22 – 5.95	1.68 ± 1.48 0.36 – 5.40	0.757
	Placebo (n=68)	1.54 ± 1.14 0.28 – 6.23	1.04 ± 0.68 0.38 – 2.81	0.097

Abbreviations: APAP-acetaminophen

Table 7-16. Comparison of Peak Alanine Aminotransferase Levels by Multiples of Baseline (Mean ± SD; Range) Stratified by Clinical Assessment of Nutritional Status at Baseline

Study [Reference]	Treatment	Normal	Clinical Malnutrition (mild or severe)	p-value
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)		Not Measured	
	Placebo (n=30)		Not Measured	
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	1.30 ± 0.45 1.00 – 2.97	1.27 ± 0.59 1.00 – 3.79	0.787
	Placebo (n=99)	1.18 ± 0.24 1.00 – 2.16	1.34 ± 0.61 1.00 – 3.19	0.259
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	1.48 ± 1.10 1.00 – 10.71	1.42 ± 1.15 1.00 – 11.48	0.624
	Placebo (n=135)	1.35 ± 0.68 1.00 – 5.15	1.39 ± 0.59 1.00 – 4.31	0.690
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	1.42 ± 0.64 0.72 – 3.64	1.34 ± 0.67 0.59 – 3.52	0.637
	Placebo (n=68)	1.23 ± 0.50 0.64 – 3.46	1.10 ± 0.35 0.81 – 2.07	0.326

Abbreviations: APAP-acetaminophen

Table 7-17. Body Mass Index in Newly Abstinent Chronic Alcoholics Enrolled in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Body Mass Index (kg/m^2) Mean ± SD Range	Body Mass Index <22 for men and <21 for women n (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	23.8 ± 3.1 19.9-32.0	8 (26.7)
	Placebo (n=30)	24.8 ± 4.8 17.7-37.7	7 (22.3)
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	23.6 ± 4.6 16.6-41.8	34 (33.3)
	Placebo (n=99)	23.4 ± 3.5 16.9-34.0	30 (30.3)
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	25.4 ± 5.1 15.4-55.3	64 (20.8)
	Placebo (n=135)	24.6 ± 3.8 17.4-38.7	28 (20.7)
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	25.0 ± 4.1 18.8-42.0	13 (17.6)
	Placebo (n=68)	24.1 ± 4.0 17.6-46.7	22 (32.4)

Abbreviations: APAP-acetaminophen

Table 7-18. Baseline Chemistry Values (Mean, ± SD, Range) in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	BUN (mg/dL)	Creatinine (mg/dL)	K+ (mmol/L)	Na+ (mmol/L)	Cl- (mmol/L)	CO_2 (mmol/L)	Glucose (non-fasting) (mg/dL)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	11 ± 4 4-27	0.8 ± 0.3 0.6-2.0	4.2 ± 0.4 3.1-5.0	137 ± 3 129-143	104 ± 4 97-110	23.5 ± 2.0 17.8-26.7	111 ± 66 60-439
	Placebo (n=30)	11 ± 5 2-28	0.8 ± 0.1 0.6-1.2	4.1 ± 0.4 3.2-4.8	137 ± 3 131-147	103 ± 4 95-112	22.5 ± 2.6 17.5-28.1	108 ± 42 62-245
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	10.7 ± 3.8 4-24	0.8 ± 0.2 0.4-1.3	4.1 ± 0.4 3.1-5.1	138.5 ± 2.4 133-145	101.0 ± 3.3 91-111	23.7 ± 2.5 18.3-28.0	97.3 ± 34.5 32-368
	Placebo (n=99)	11.5 ± 4.5 4-40	0.8 ± 0.3 0.5-2.8	4.2 ± 0.4 3.5-5.3	138.8 ± 2.9 132-147	101.6 ± 3.6 92-110	23.1 ± 3.3 17.4-30.1	96.0 ± 24.1 59-227
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	10.8 ± 3.6 3-25	0.8 ± 0.2 0.4-1.3	4.3 ± 3.1 2.5-45.0	138.9 ± 2.8 129-147	102.0 ± 3.3 88-111	24.2 ± 3.4 17-37	114.4 ± 62.9 58-888
	Placebo (n=135)	11.2 ± 3.9 4-24	0.8 ± 0.1 0.4-1.2	4.0 ± 0.4 3.0-5.0	139.7 ± 2.6 134-149	102.6 ± 3.4 94-111	25.6 ± 17.6 16-225	104.0 ± 29.4 63-266
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	10.7 ± 5.3 3.00-33.88	0.8 ± 0.1 0.50-1.19	4.1 ± 0.4 2.7-5.5	139.9 ± 3.4 131-148	101.0 ± 4.1 91-110	25.3 ± 3.7 18-35	105.8 ± 30.8 54.0-212.4
	Placebo (n=68)	10.6 ± 4.3 1.96-24.00	0.8 ± 0.1 0.40-1.20	4.6 ± 4.1 3.1-38.0	140.5 ± 2.9 132-146	102.2 ± 3.6 94-114	25.5 ± 3.5 18-33	104.2 ± 48.2 55.0-433.0

Abbreviations: APAP-acetaminophen, BUN-blood urea nitrogen

Table 7-19 Baseline Hematology Values (Mean, ± SD, Range) in Acetaminophen, Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	RBC (M/µL)	WBC (K/µL)	Platelets (K/µL)	Hemoglobin (gm/dL)	Hematocrit (%)
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured	6.5 ± 1.6 3.3-10.0	223 ± 82 36-395	14.9 ± 1.3 12.3-17.1	43.7 ± 3.7 35.4-50.6
	Placebo (n=30)	Not Measured	7.3 ± 2.8 3.5-14.5	218 ± 84 18.4-364	15.1 ± 1.1 12.4-17.7	43.8 ± 3.1 37.1-53.2
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	Not Measured	6.6 ± 2.2 3.4-18.4	235.6 ± 74.2 898-396	15.0 ± 1.7 9.1-18.4	43.6 ± 4.5 30.1-54.5
	Placebo (n=99)	Not Measured	6.8 ± 2.7 3.1-23.0	221.1 ± 67.4 54-427	15.0 ± 1.7 9.5-19.6	43.8 ± 4.6 30.7-55.2
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	4.58 ± 0.52 2.79-6.27	6.6 ± 2.2 2.2-14.9	235.3 ± 80.3 60-503	14.6 ± 1.5 8.6-17.6	42.7 ± 4.2 27.5-53.0
	Placebo (n=135)	4.57 ± 0.50 3.26-5.71	6.4 ± 2.2 2.3-17.1	241.7 ± 89.8 67-515	14.5 ± 1.5 9.6-17.2	42.5 ± 4.3 28.7-50.8
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	4.58 ± 0.52 3.13-5.92	6.1 ± 1.9 2.82-12.60	235.4 ± 85.4 46-440	14.8 ± 1.8 8.2-20.3	44.0 ± 5.2 27.8-61.7
	Placebo (n=68)	4.67 ± 0.54 3.08-5.84	6.0 ± 2.0 3.00-11.50	251.1 ± 81.1 115-454	14.6 ± 1.6 9.4-17.8	43.6 ± 4.2 29.3-52.4

Abbreviations: APAP-acetaminophen, RBC-red blood cell count, WBC-white blood cell count

Table 7-20. Demographics of Study Populations

Study	Pilot Two-Day [1]		Two-Day [2]		Three-Day [84]		Five-Day [85]	
	APAP	Placebo	APAP	Placebo	APAP	Placebo	APAP	Placebo
Males/Females (n)	30/0	29/1	91/11	89/10	284/24	128/7	67/7	64/4
Age, y								
Mean±SD	45.0 ± 7.0	42.5 ± 8.1	43.9 ± 8.6	45.0 ± 8.2	43± 9	44 ± 8	45.7 ± .4	46.8 ± 8.3
Range	(31-59)	(26-58)	(27-68)	(28-70)	(18-72)	(20-65)	(21-77)	(26-64)
Ethnicity, n(%)								
Caucasian	13 (43)	10 (33)	50 (49)	52 (53)	156 (51)	68 (50)	38 (51)	28 (41)
Black	8 (27)	4 (13)	27 (26)	20 (20	49 (16)	16 (12)	3 (4)	11 (16)
Hispanic	9 (30)	16 (53)	17 (17)	19 (19)	45 (15)	22 (16)	16 (22)	12 (18)
Native American	0	0	5 (5)	8 (8)	49 (16)	23 (17)	12 (16)	9 (13)
Other	0	0	3 (3)	0	15 (5)	6 (4)	5 (7)	8 (12)

Abbreviations: APAP=acetaminophen

Table 7-21. Mean Changes from Baseline (Confidence Intervals) for AST (IU/L) in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	-8.1 (-9.9, -6.3)	Not Measured	1.6 (-0.6, 3.8)	Not Measured	Not Measured	Not Measured
	Placebo (n=30)	1.7 (-0.6, 3.8)	Not Measured	-2.1 (-4.4, 0.2)	Not Measured	Not Measured	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	-6.9 (-9.8, -4.0)	Not Measured	-2.2 (-6.6, 2.2)	Not Measured	Not Measured	Not Measured
	Placebo (n=99)	-3.0 (-6.7, 0.6)	Not Measured	-4.1 (-9.3, 1.2)	Not Measured	Not Measured	Not Measured
Three-Day [84]	APAP 4 g/d x 3 days (n=258)	-10.9 (-13.7, -8.0)	-11.9 (-16.1, -7.7)	-9.4 (-13.8, -5.1)	-2.7 (-6.9, 1.6)	Not Measured	Not Measured
	Placebo (n=114)	-5.6 (-10.9, -0.4)	-4.8 (-10.9, 1.3)	-6.5 (-11.7, -1.3)	-7.3 (-13.0, -1.6)	Not Measured	Not Measured
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	-12.2 (-16.7, -7.6)	Not Measured	-8.8 (-16.8, -0.7)	Not Measured	-9.5 (-19.9, 1.0)	-9.0 (-16.7, -1.2)
	Placebo (n=68)	-11.4 (-14.9, -7.8)	Not Measured	-12.4 (-17.3, -7.4)	Not Measured	-14.8 (-20.4, -9.2)	-17.3 (-23.1, -11.4)

Abbreviations: APAP-acetaminophen, AST-aspartate aminotransferase

Table 7-22. Mean Changes from Baseline (Confidence Intervals) for ALT (IU/L) in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	Not Measured	Not Measured	8.7 (6.9, 10.5)	Not Measured	Not Measured	Not Measured
	Placebo (n=30)	Not Measured	Not Measured	10.0 (7.0, 13.0)	Not Measured	Not Measured	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	-1.6 (-3.9, 0.7)	Not Measured	5.7 (1.1, 10.4)	Not Measured	Not Measured	Not Measured
	Placebo (n=99)	0.9 (-1.7, 3.6)	Not Measured	5.4 (-0.9, 11.0)	Not Measured	Not Measured	Not Measured
Three-Day [84]	APAP 4 g/d x 3 days (n=258)	-3.6 (-6.1, -1.1)	-3.6 (-6.4, -0.7)	-0.7 (-3.9, 2.6)	7.8 (3.9, 11.6)	Not Measured	Not Measured
	Placebo (n=114)	-1.8 (-4.9, 1.3)	1.1 (-2.7, 4.9)	4.7 (0.6, 8.9)	8.0 (3.0, 13.1)	Not Measured	Not Measured
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	-6.5 (-9.3, -3.7)	Not Measured	-2.3 (-8.3, 3.7)	Not Measured	5.8 (-1.0, 12.6)	11.7 (5.4, 18.1)
	Placebo (n=68)	-5.2 (-7.5, -3.0)	Not Measured	-3.0 (-8.0, 2.0)	Not Measured	1.9 (-4.3, 8.0)	1.8 (-4.5, 8.2)

Abbreviations: APAP-acetaminophen, ALT-alanine aminotransferase

Table 7-23. Mean Changes from Baseline (Confidence Intervals) for INR in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	-0.04 (-0.07, -0.004)	Not Measured	-0.05 (-0.08, -0.01)	Not Measured	Not Measured	Not Measured
	Placebo (n=30)	-0.04 (-0.08, -0.01)	Not Measured	-0.02 (-0.08, 0.02)	Not Measured	Not Measured	Not Measured
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	-0.01 (-0.02, 0.002)	Not Measured	-0.01 (-0.02, 0.01)	Not Measured	Not Measured	Not Measured
	Placebo (n=99)	-0.02 (-0.04, -0.01)	Not Measured	-0.002 (-0.03, 0.02)	Not Measured	Not Measured	Not Measured
Three-Day [84]	APAP 4 g/d x 3 days (n=258)	-0.02 (-0.03, -0.01)	-0.03 (-0.03, -0.02)	-0.02 (-0.03, -0.02)	-0.02 (-0.03, -0.01)	Not Measured	Not Measured
	Placebo (n=114)	-0.02 (-0.03, -0.01)	-0.03 (-0.04, -0.01)	-0.03 (-0.04, -0.02)	-0.02 (-0.03, -0.01)	Not Measured	Not Measured
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	0.02 (0.01, 0.04)	Not Measured	-0.01 (-0.02, 0.01)	Not Measured	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
	Placebo (n=68)	-0.01 (-0.02, 0.01)	Not Measured	-0.02 (-0.04, 0.00)	Not Measured	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.03)

Abbreviations: APAP-acetaminophen, INR- international normalized ratio

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Table 7-24. Mean AST/ALT ratios in Subjects with a Baseline Ratio of >2.0 in Acetaminophen Prospective, Randomized Clinical Studies

Study [Reference]	Treatment	Baseline mean (confidence interval) n	Endpoint mean (confidence interval) n
Pilot Two-Day [1]	APAP 4 g/d x 2 days (n=30)	2.8 (2.6, 3.0)	2.5 (2.3, 2.8)
	Placebo (n=30)	2.3 (2.1, 2.5)	1.8 (1.7, 1.9)
Two-Day [2]	APAP 4 g/d x 2 days (n=102)	2.36 (2.13, 2.58) 5	1.51 (1.23, 1.80) 5
	Placebo (n=99)	2.41 (2.11, 2.71) 8	1.54 (1.16, 1.93) 8
Three-Day [84]	APAP 4 g/d x 3 days (n=308)	2.51 (2.30, 2.71) 30	1.85 (1.50, 2.21) 26
	Placebo (n=135)	2.48 (2.25, 2.71) 16	1.62 (1.40, 1.84) 11
Five-Day [85]	APAP 4 g/d x 5 days (n=74)	2.51 (2.14, 2.89) 12	1.84 (1.39, 2.29) 10
	Placebo (n=68)	2.23 (2.05, 2.40) 4	0.90 (0.63, 1.16) 4

Abbreviations: APAP-acetaminophen, ALT-alanine aminotransferase, AST-aspartate aminotransferase

Table 7-25. Demographic and Baseline Characteristics of Subjects in the Ten-Day Acetaminophen Study

	Acetaminophen (n=104)	**Control (n=52)**
Age (y), mean (SD)	32.6 (9.8)	34 .0 (13.4)
Range	21-64	22-79
Male, No. (%)	54 (52)	30 (58)
Ethnicity, No. (%)		
Non-Hispanic White	90 (87)	44 (85)
Hispanic	8 (8)	1 (2)
African American	4 (4)	1 (2)
Asian	1 (1)	4 (8)
Mixed or Oher	1 (1)	2 (2)
Body mass index, No. (%)		
Underweight (BMI<18.5 kg/m^2)	1 (1)	0 (0)
Normal (18.5 to 25.0 kg/m^2)	62 (60)	35 (67)
Overweight (25.1 to 30 kg/m^2)	30 (29)	13 (25)
Obese (>30 kg/m^2)	11 (11)	4 (8)
Proportion that reported previous use of APAP, No. (%)	63 (61)	35 (67)
Daily drinks during study, mean (SD)	2.24 (0.92)	2.08 (0.73)
Range	0.70 – 4.80	0.70 – 3.80
Doses taken at appropriate time interval, %	68%	73%

Table 7-26 Mean (± SD, Range) Values for ALT, AST, Total Bilirubin, Alkaline Phosphatase, and Total Protein in Ten-Day Study, Completed Group

	Acetaminophen (n=100)			Control (n=50)		
Variable	**Baseline**	**Day 4**	**Day 11**	**Baseline**	**Day 4**	**Day 11**
ALT (IU/L)	21.3±7.6 11-49	21.0±7.5 10-57	30.0±18.6 8-128	22.4±8.2 12-49	21.7±8.2 12-44	21.6±7.9 12-47
AST (IU/L)	21.5±5.6 9-41	22.6±5.8 12-47	28.3±24.7 13-254	22.0±5.8 14-50	22.7±8.9 12-65	21.8±5.3 13-37
Total Bilirubin (µmol/L)	10.2±6.50 3.4-39.4	9.9±5.7 3.4-34.3	10.7±7.5 3.4-46.2	9.8±5.1 3.4-30.8	10.2±5.8 5.1-41.1	10.7±7.6 1.7-46.2
Alkaline phosphatase range	68.1±17.9 32-116	65.8±17.6 32-115	66.2±17.5 33-118	69.0±16.9 40-102	68.6±16.1 41-103	68.1±15.5 40-102
Total protein (g/L)	73±9.6 62-146	72±4.2 60-82	73±3.9 62-82	73±9.5 64-131	72±3.5 66-79	72±3.6 64-83

Table 7-27. Mean Changes from Baseline for ALT, AST, Total Bilirubin, Alkaline Phosphatase and Total Protein in 10 Day Study

	Acetaminophen Mean (95% CI)		Control Mean (95% CI)	
Variable	**Baseline to Day 4**	**Baseline to day 11**	**Baseline to Day 4**	**Baseline to day 11**
ALT (IU/L)	-0.3 (-1.3 to 0.7)	8.7 (5.4 to 12.0)	-0.3 (-1.3 to 0.7)	8.7 (5.4 to12.0)
AST (IU/L)	1.1 (0.2 to 2.1)	6.7 (1.9 to 11.2)	1.1 (0.2 to 2.1)	6.7 (1.9 to 11.2)
Total Bilirubin (µmol/L)	0.34 (-0.34 to 1.03)	0.34 (-0.51 to 1.20)	0.34 (-0.34 to 1.03)	0.34 (-0.51 to 1.20)
Alkaline phosphatase (IU/L)	2.3 (1.2 to 3.3)	1.9 (0.6 to 3.2)	2.3 (1.2 to 3.3)	1.9 (0.6 to 3.2)
Total protein (g/L)	-1.0 (-3.0 to 1.0)	-0.3 (-2.0 to 2.0)	-1.0 (-3.0 to 1.0)	-0.3 (-2.0 to 2.0)

7.10 Reference List

1. Kuffner EK, Bogdan GM, Dart RC. Evaluation of hepatotoxicity in alcoholics from therapeutic dosing of acetaminophen. J Toxicol 1997;35:561(abstract).

   Report Synopsis for Evaluation of hepatotoxicity in alcoholics from therapeutic dosing of acetaminophen, 1997, RMPC.

2. Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminohpen on the liver of alcoholic patients. A randomized, double-blind, placebo-controlled trial. Arch Intern Med 2001;161:2247-2252.

   Report Synopsis for Effect of maximal daily dose of acetaminophen on the liver of alcoholic patients, 2001, RMPC.

3. Lauterburg BH. Analgesics and glutathione. *Am J Ther*. 2002;9:225-232.

4. Lauterburg BH, Velez ME. Glutathione deficiency in alcoholics: risk factor for paracetamol hepatotoxicity. Gut 1988;29:1153-1157.

5. Smilkstein M.J., Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976-1985) N Engl J Med 1988;319: 1557-1562.

6. Prescott LF. Paracetamol, alcohol and the liver. Br J Clin Pharmacol 2000;49:291-301.

7. Maddrey WC. Hepatic effects of acetaminophen. Enhanced toxicity in alcoholics. J Clin Gastroenterol 1987;9:180-185.

8. Seeff LB, Cuccherini BA, Zimmerman HJ, et al. Acetaminophen hepatotoxicity in alcoholics. A therapeutic misadventure. Ann Intern Med 1986;104:399-404.

9. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: Analysis of instances of therapeutic misadventure [published erratum appears in Hepatology 1995;22:1898] Hepatology 1995;22:767-773.

10. NDAC meeting September 19-20, 2002 transcript, http://www.fda.gov/ ohrms/dockets/ac/02/transcripts /3882T1.htm and slides, http://www.fda.gove/ohrms /dockets/ac/02/slides /3882S1_05_Nourjah-Ahmad-Karwoski_files/frame.htm.

11. Lowenstein SR. Medical record reviews in emergency medicine: The blessing and the curse. Ann Emerg Med 2005;45:452-455.

12. Bristol N. Report slams US FDA's drug safety reform efforts. Lancet 2007;369:1072.

13. Holubek WJ, Kalman S, Hoffman RS. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2006;43:880; author reply 882.

14. Montague RED, Grace RF, Lewis JH, et al. Urine drug screens in overdose patients do no contribute to immediate clinical management. Ther Drug Monitor 2001;23:47-50.

15. Gyamlani GG, Parikh CR. Acetaminophen toxicity: suicidal vs. accidental. Crit Care. 2002;6:155-159.

16. Makin AJ, Wendon J, Williams R. A 7-year experience of acetaminophen-induced hepatotoxicity (1987-1993). Gastroenterology 1995;109:1907-1916.

17. Hensrud DD, Engle DD, Scheitel SM. Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination. Mayo Clin Proc. 1999;74:443-447.

18. Ayonrinde OT, Phelps GJ, Hurley JC, et al. Paracetamol overdose and hepatotoxicity at a regional Australian hospital: a 4-year experience. Internal Med J 2005;35:655-60.

19. Bray GP, Mowat C, Muir DF, et al. The effect of chronic alcohol intake on prognosis and outcome in paracetamol overdose. Human Exp Toxicol 1991;18:435-438.

20. Makin A, Williams R, Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. Q J Med 2000;93:341-349.

21. Schiodt FV, Rochling FA, Casey DL, et al. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997;337:1112-1117.

22. Larson AM, Polson J, Fontana RJ et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42:1364-1372.

23. Broughan TA, Soloway RD. Acetaminophen hepatotoxicity. Dig Dis Sci 2000;45:1553-1558.

24. Matsika MD, Moore N. Intentional drug overdoses: Validity of the information sources on drugs in comparison with plasma data. Thérapie 1999;54:273 (abstract).

25. 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;23:47-50.

26. 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;22:749-752.

27. D'Argembeau A, Van Der Linden M, Verbanck P, et al. Autobiographical memory in non-amnesic alcohol-dependent patients. Psychol Med 2006;36:1707-1715.

28. Heffernan TM, Bartholomew J. Does excessive alcohol use in teenagers affect their everyday prospective memory. J Adolesc Health 2006;39:138-140.

29. Perry PJ, Argo TR, Barnett MJ, et al. The association of alcohol-induced blackouts and grayouts to blood alcohol concentrations. J Forensic Sci 2006;51:896-899.

30. Stange KC, Zyansky SJ, Smith TF, et al. How valid are medical records and patient questionnaires for physician profiling and health services research? A comparision with direct observation of patient visits. Med Care 1998;36:851-867.

31. Horowitz RI, Yu EC. Assessing the reliability of epidemiologic data obtained from medical records. J Chron Dis 1984;37:825-831.

32. Boyd NF, Pater JL, Ginburg AD, et al. Observer variation in the classification of the information from medical records. J Chron Dis 1979;32:327-332.

33. Gilbert EH, Lowenstein SR, Koziol-McLain J, et al. Chart reviews in emergency medicine research: Where are the methods. Ann Emerg Med 1996;27:305-308.

34. Worster A, Bledsoe RD, Cleve P, et al. Reassessing the methods of medical record review studies in emergency medicine research. Ann Emerg Med 2005;45:448-451.

35. Badcock D, Kelly AM, Kerr D, et al. The quality of medical record review studies in the international emergency medicine literature. Ann Emerg Med 2005;45:444-447.

36. Brody DS. Physician recognition of behavioral, psychological and social aspects of medical care. Arch Intern Med 1980;140:1286-1289.

37. Schmidt LE, Dalhoff K, Poulsen HE. Acute versus chronic alcohol consumption in acetaminophen-induced hepatotoxicity. Hepatology 2002;35:876-882.

38. Poulsen HE, Dalhof K, Loft S, et al. Acute and chronic alcohol intake influence paracetamol hepatotoxicity in man. J Hepatology 1988;7(suppl 1):S164 (abstract).

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

40. Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med 1981;141:380-385.

41. Rumack BH. Acetaminophen overdose in young children. Am J Dis Child 1984;138:428-433.

42. Read RB, Tredger JM, Williams R. Analysis of factors responsible for continuing mortality after paracetamol overdose. Human Toxicol 1986;5:201-206.

43. Schiodt FV, Lee WM, Bondesen S, et al. Influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose. Aliment Pharmacol Ther 2002;16:707-715.

44. Bray GP, Mowat C, Muir DF, et al. The effect of chronic alcohol intake on prognosis and outcome in paracetamol overdose. Human Exp Toxicol 1991;18:435-438.

45. Brotodihardjo AE, Batey RG, Farrell GC, et al. Hepatotoxicity from paracetamol self-poisoning in western Sydney: a continuing challenge. Med J Australia 1992;157:382-385.

46. Wang K, Huang YS, Deng JF, et al. Characteristics and risk factors of acetaminophen-induced hepatitis in Taiwan. Zhonghua Yi Xue Za Zhi 1999;62:369-375.

47. Gyamlani GG, Parikh CR. Acetaminophen toxicity: Suicidal vs accidental. Crit Care 2002;6:155-159.

48. Smilkstein MJ, Rumack BH. Chronic ethanol use and acute acetaminophen overdose toxicity. J Toxicol Clin Toxicol 1998;36:476 (abstract).

49. Schmidt LE, Dalhoff K. Concomitant overdosing of other drugs in patients with paracetamol poisoning. Br J Clin Pharmacol 2002;53:535-541.

50. Kumar S, Rex DK. Failure of physicians to recognize acetaminophen hepatotoxicity in chronic alcoholics. Arch Intern Med 1991;151:1189-1191.

51. NDAC meeting September 19-20, 2002 transcript, http://www.fda.gov/ohrms/dockets/ac/02/trascripts/3882T1.htm and slides, http://www.fda.gov/ohrms/dockets/ac/02/slides/3882S1_04_Lee_files/frame.htm).

52. Chen LH, Baker SP, Guohua L. Drinking history and risk of fatal injury: comparison among specific injury causes. Accid Anal Prev 2005;37:245-251.

53. MacDonald S, Cherpitel CJ, DeSouza A, et al. Variations of alcohol impairment in different types, causes and contexts of injuries: Results of emergency room studies from 16 countries. Accident Anal Prevent 2006;38:1107-1112.

54. Anda RF, Williamson DF, Remington PL. Alcohol and fatal injuries among US adults-findings from the NHANES I epidemiologic follow-up study. JAMA 1988;260:2529-2532.

55. George S, Rogers RD, Duka T. The acute effect of alcohol on decision making in social drinkers. Psychopharmacology 2005;182:160-169.

56. Guohua Li, Smith G, Baker SP. Drinking behavior in relation to cause of death among US adults. Am J Pub Health 1994;84:1402-1406.

57. McLeod R, Stockwell T, Rooney R, et al. The influence of extrinsic and intrinsic risk factors on the probability of sustaining an injury. Accident Anal Prev 2003;35:71-80.

58. Coffin PO, Galea S, Ahern J, et al. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in NYC, 1990-1998 Addiction. 2003;98:739-747.

59. Davidson P, Koziol-McLain J, Harrison L, et al. Intoxicated ED patients: A 5-year follow-up of morbidity and mortality. Ann Emerg Med 1997;30:593-597.

60. Li G, Smith GS, Baker SP. Drinking behavior in relation to cause of death among US adults. Am J Pub Health 1994;84:1402-1406.

61. Levy DT, Mallonee S, Miller TR, et al. Alcohol involvement in burn, submersion, spinal cord and brain injuries. Med Sci Monitor 2004;10:17-24.

62. Guo H, Eskridge KM, Christesen D, et al. Statistical adjustment for misclassification of seat belt and alcohol use in the analysis of motor vehicle accident data. Accident Analysis Prevent 2007;39:117-124.

63. Sorock GS, Chen LH, Gonzalgo SR, et al. Alcohol-drinking history and fatal injury in older adults. Alcohol 2006;40:193-199.

64. Pirkola SP, Isometsä ET, Heikkinen ME, et al. Suicides of alcohol misusers and non-misusers in a nationwide population. Alcohol Alcoholism 2000;35:70-75.

65. Miller JW, Naimi TS, Brewer RD, et al. Binge Drinking and Associated Health risk Behaviors Among High School Students. Pediatrics 2007;119:76-85.

66. APA Practice Guidelines for the Assessment and Treatment of Patients with Suicidal Behaviors. Amer J Psychiatry 2004; 160 (11).

67. Petronis KR, Samuels JF, Moscicki EK, Anthony JC. An Epidemiologic Investigation of Potential Risk Factors of Suicide Attempts. Soc Psychiatry Psychiatr Epidemiol 1990; 25:193-199.

68. Ohberg A, Vuori E, Ojanpera I, Lonngvist J. Alcohol and Drugs in Suicides (abstract). Br J Psychiatry 1996; 169:75-80.

69. Hayward L, Zubrick SR, Silburn S. Blood Alcohol Levels in Suicide Cases. J Epidemiol Community Health 1992; 46:256-260.

70. Suokas J, Lonnqvist J. Suicide Attempts in which Alcohol is Involved: A Special Group in General Hospital Emergency Rooms. Acta Psychiatr Scand 1995; 91:36-40.

71. Suominen KH, Isometsa ET, Henriksson MM, Ostamo AI, Lonnqvist JK. Treatment Received by Alcohol-Dependent Suicide Attempters. Acta Psychiatr Scand 1999; 99:214-219.

72. Marzuk PM, Mann JJ. Suicide and Substance Abuse. Psychiatr Ann 1988; 18:639-645.

73. Borges G, Rosovsky H. Suicide Attempts and Alcohol Consumption in an Emergency Room Sample. J Stud Alcohol 1996; 57:543-548.

74. McGrath J. A Survey of Deliberate Self-Poisoning. Med J Aust 1989; 150:317-318, 320-321, 324.

75. Varadaraj R, Mendonca J. A Survey of Blood-Alcohol Levels in Self-Poisoning Cases. Adv Alcohol Subst Abuse 1987; 7:63-69.

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

77. Bailey and Dart RC, Pharmacotherapy, (In press)

78. Thummel KE, Slattery JT, Ro H, et al. Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults. Clin Pharmacol Ther 2000;67:591-599.

79. Critchley JAJH, Cregeen RJ, Balali-mood M, Pentland B, Prescott LF. Paracetamol metabolism in heavy drinkers. Preceedings Brit Pharm Soc. 1982;13:276P-277P.

80. 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

81. Skinner MH, Matano R, Hazle W, Blaschke TF. Acetaminophen metabolism in recovering alcoholics. Meth Find Exp Clin Pharmacol 1990;12:513-515.

82. Critchley JAJH, Lau GNS, Leung NWY. Paracetamol metabolism in Chinese alcoholics. Hepatol 1990;12:398 (Abstract).

83. Chern I, Brent J, Slattery J, Ritvo J, Kalhorn T, *et al*. Is it safe to give acetaminophen to alcoholics? A metabolic study. Vet Human Toxicol 1993;35:36 (Abstract)

84. Kuffner EK, Green JL, Bogdan GM, et al. Hepatic function of alcoholic patients is not affected by the maximum daily doses of acetaminophen for three consecutive days – a multicenter study. Awaiting publication.

    Report Synopsis for Hepatic function of alcoholic patients is not affected by the maximum daily doses of acetaminophen for three consecutive days – a multicenter study, 2006, RMPC.

85. Green JL, Kuffner EK, Bogdan GM. Hepatic function in alcoholics throughout 5 days of maximal therapeutic dosing of acetaminophen (APAP) (abstract). Clin Toxicol 2005;43:683.

    Report Synopsis for Hepatic function in alcoholics throughout 5 days of maximal therapeutic dosing of acetaminophen (APAP), 2007, RMPC.

86. Bartels SA et al. Does maximal therapeutic dosing of acetaminophen perturb hepatic biomarkers in recently abstinent alcoholics? (abstract). Clin Toxicol 2005;43:680-681.

87. Black M, Raucy J. Acetaminophen, alcohol, and cytochrome P-450. Ann Intern Med 986;104:427-429.

88. Thummel KE, Slattery JT, Nelson SD. Mechanism by which ethanol diminishes the hepatotoxicity of acetaminophen. J Pharmacol Exper Ther 1988;24:129-136.

89. Slattery JT, Nelson SD, Thummel KE. The complex interaction between ethanol and acetaminophen. Clin Pharmacol Ther 1996;60:241-246.

90. Banda PW, Quart BD. The effect of mild alcohol consumption on the metabolism of acetaminophen in man. Res Comm Chem Pathol Pharmacol 1982;38:57-70.

91. Shaw S, Rubin K, Lieber CS. Depressed hepatic glutathione and increased diene conjugates in alcoholic liver disease. Dig Dis Sci 1983;28:585-90.

92. Lucus D, Menez C, Girre C, et al. Decrease in cytochrome P4502E1 as assessed by the rate of chlorzoxazone hydroxylation in alcoholics during the withdrawal phase. Alcoholism: Clin Exp Res 1995;19:362-366.

93. Oneta CM, Lieber CS, Li J, et al. Dynamics of cytochrome P4502E1 activity in man: induction by ethanol and disappearance during withdrawal phase. J Hepatol 2002;36:47-52.

94. Lieber CS. Cytochrone P-4502E1: Its physiological and pathological role. Physiol Rev 1997;77:517-543.

95. Diehl AM. Liver disease in alcohol abusers: clinical perspective. Alcohol 2002;27:7-11

96. O'Conner PG, Schottenfield RS. Patients with medical problems. N Engl J Med 1998;338;592-602.

97. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am J Psychiatry 974;131:1121-1123.

98. Fiellin DA, Reid C, O'Connor PG. Screening for alcohol problems in primary care. A systematic review. Arch Intern Med 2000;160:1977-1989.

99. Pokorney AD, Miller BA, Kaplan HG. The brief MAST. A shortened version of the Michigan Alcoholism Screening Test. Am J Psychiatry 1972;129:342-345.

100. Diehl AM. Liver disease in alcohol abusers. Alcohol 2002;27:7-11.

101. Sillanaukee P, Aalto M, Seepa K. Carobhydrate deficient transferring and conventional alcohol markers as indicators for brief intervention among heavy drinkers in primary health care. Alcohol Clin Res 1998;22:892-896.

102. Allen JP, Sillanaukee P, Strid N, et al. Biomarkers of heavy drinking. In Assessing alcohol problems. A guide for clinicians and researchers. Available at: http://pubs.niaaa.nih.gov/publications/Assesing%20Alcohol/biomarkers.htm. Assessed April 1, 2007.

103. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. JAMA 1997 278:144-151.

104. Mayo-Smith MF, Beecher LH, Fisher TL, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004;164:1405-1412.

105. Caetano R, Clark CL, Greenfield TK. Prevalence, trends, and incidence of alcohol withdrawal symptoms. Analysis of general population and clinical samples. NIAA's Epidemiologic Bulletin No 38. 1998;22:73-79.

106. Halstead CH. Nutrition and alcoholic liver disease. Sem Liver Dis 2004;24:289-304.

107. Baker JP, Detsy AS, Wesson DE. A comparison of clinical judgment and objective measurements. N Engl J Med 1982;306:969-72.

108. Committee on Diet and Health, Food and Nutrition Board, Commission on Life Sciences, National Research Council Diet and Health. Implications for reducing chronic disease risk. Washington DC: National Academy Press, 1989.

109. Shetty P, James WPF. Body mass index: a measure of chronic energy deficiency in adults. FAO Food and Nutrition Paper No. 56. Rome: Food and Agriculture Organization 1994. Available at http://www.fao.org/docrep/t1970e/t1970e00.htm.

110. Rapp-Kesek D, Ståhle E, Karlsson T. Body mass index and albumin in the preoperative evaluation of cardiac surgery patients. Clin Nutr 2004;23:1398-1404.

111. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, Part I: History, examination, body composition, and screening tools. Nutrition 2000;16:50-63.

112. Merck Manual. Undernutrition. Available at: http://www.merck.com/mmpe/sec01/ch002/ch002a.html#sec01-ch002-ch002a-98. Assessed April 1, 2007.

113. Watanabe A, Mtasuzaki S, Moriwaki H, et al. Problems in serum albumin measurement and clinical significance of albumin microheterogeneity in cirrhotics. Nutrition 2004;20:351-357.

114. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. Clin Toxicol 2002;40:3-20.

115. Lee AM, Joshi M, Yue J, et al. Phenobarbital induces monkey brain CYP2E1 protein but not hepatic CYP2E1, in vitro or in vivo chlorzoxazone metabolism. Eur J Pharmacol 2006;552:151-158.

116. 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.

117. Frye RF, Branch RA. Effect of chronic disulfiram administration on the activities of CYP1A2, CYP2C19, CYP2D6, CYP2E1, and N-acetyltransferase in healthy human subjects. Br J Clin Pharmacol 2002;53:155-162.

118. Manyike PT, Kharasch ED, Kalhorn TF, et al. Contribution of CYP2E1 and CYP3A4 to acetaminophen reactive metabolite formation. Clin Pharmacol Ther 2000;67:275-282.

119. Dart, RC. Rocky Mountain Poison and Drug Center, Colorado. *personal communication of data not published*

120. Heard K, Green GL, Bailey JE, et al. A randomized trial to determine the change in ALT during 10 days of acetaminophen administration in subjects who consume moderate amounts of alcohol. Not published.

Report Synopsis for A randomized trial to determine the change in ALT during 10 days of acetaminophen administration in subjects who consume moderate amounts of alcohol, 2006, RMPC.

121. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily. A randomized controlled trial. JAMA 2006;296:87-93.

122. Kuffner EK, Temple AR, Cooper KM, et al. Retrospective analysis of transient elevations in alanine aminotransferase during long-term treatment with acetaminophen in osteoarthritis clinical trials. Curr Med Res Opinion. 2006;22:2137-2148.

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8 MCNEIL'S EDUCATIONAL INITIATIVES ENCOURAGE RESPONSIBLE USE OF OTC ANALGESIC PRODUCTS

This section provides a summary of recent available information regarding trends in consumer medication use of analgesics and further details about McNeil's wide-reaching labeling and educational initiatives to encourage responsible use of OTC analgesics.

8.1 FDA Comments from the Proposed Rule

At the September 19, 2002 Nonprescription Drug Advisory Committee (NDAC) meeting, participants were asked to consider what additional measures could be taken to better ensure that prescribers and others are aware of the potential risks associated with exceeding the recommended dose of prescription or OTC drug products containing acetaminophen and with using multiple drug products containing acetaminophen. In FDA's proposed rule, FDA summarized the following points from that meeting:

- "NDAC concluded that FDA and manufacturers have a joint responsibility to reduce the occurrence of unintentional overdoses from acetaminophen. NDAC considered it essential that consumer and professional education programs heighten awareness of risk, particularly to certain populations." [71 FR 77324]
- "NDAC stated that many physicians and pharmacists may not be aware of the risks of unintentional overdose. NDAC added that, along with consumer education, professional programs are important, because prescription products containing acetaminophen are widely used. Education of pharmacists would be needed to support the use of additional labeling information (stick-on labels, etc.) attached to prescription containers. NDAC stated that auxiliary labeling is critical to conveying information that the prescription product contains acetaminophen." [71 FR 77324]
- "NDAC also expressed concern about the lack of standardized, pediatric dosage information, especially for infants under 2 years of age." [71 FR 77324]

Additionally, in FDA's Proposed Rule, "FDA encourages manufacturers of these products to undertake education initiatives regarding safe use of OTC products containing acetaminophen and NSAIDs." [71 FR 77331]

8.2 McNeil's Position

McNeil agrees with FDA about the important role of labeling and education to help minimize misuse of OTC analgesic products. McNeil has a long history of voluntarily implementing labeling and educating consumer and healthcare professionals about appropriate use of OTC analgesics.

8.3 Key Points from McNeil's Response

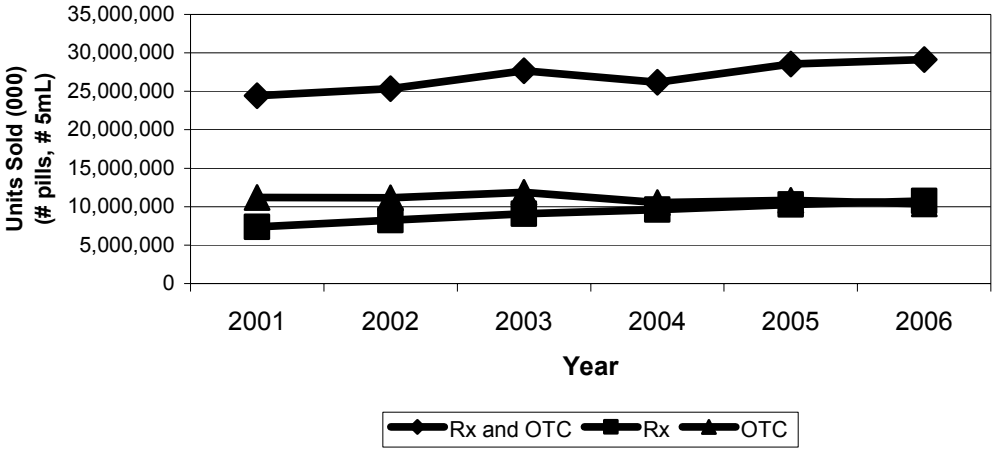
- In the United States (US), acetaminophen-containing products (OTC and prescription) are among the most frequently used medications. In any given week, some 20-23% of adults (45 million) report using acetaminophen-containing products.
- Recent medication use surveys suggest that the vast majority of consumers report using acetaminophen within the labeled OTC daily dose.
- The container labels on most prescription acetaminophen-combination products are inadequate. In a recent survey of consumers who had a prescription bottle for an acetaminophen-combination product in their home, the majority of participants reported that the label on their prescription container had the abbreviation "APAP" and they did not know what the abbreviation represented. Label warnings about taking more than the recommended dose and taking with other acetaminophen products were reported at best by 37% of participants as appearing on their prescription acetaminophen-combination product bottle.
- McNeil has a long history of, and remains committed to, developing, supporting, and implementing educational initiatives aimed at focusing 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 strongly urges FDA to respond to the Citizen Petition filed in 1999 to expand dosing directions on OTC pediatric acetaminophen product labeling to include dosing for children under two years of age.
- McNeil encourages FDA, Pharmacy and Medical Associations, and other interested stakeholders to work to improve container labels of prescription acetaminophen-combination products, to increase consumer understanding that prescription acetaminophen-combination products contain the active ingredient "acetaminophen", and to improve the education of healthcare professionals on these matters.

8.4 Recent Trends in Consumer Medication Use of Analgesic Products

Based on IMS Health, National Sales Perspectives data, acetaminophen-containing products (OTC and prescription) are among the most frequently used medicines throughout the US [1]. As shown in Figure 8.1, in the US, acetaminophen-containing products had a compound annual growth rate (CAGR) of 4% over the period of 2001 to 2006. The OTC market (volume) was fairly stable with a CAGR of -2%. In contrast, the prescription acetaminophen-combination products showed a clear increase during the same period with a CAGR of 8%. Hydrocodone-acetaminophen combination products account for much of the growth of prescription acetaminophen-combination products.

Figure 8.1 OTC and Prescription Acetaminophen Sales in the US by Year



The Slone Survey™ (http://www.bu.edu/slone/), which has surveyed medication use in the US on an ongoing basis since 1998, provides the most currently available nationally representative information on medication use. The Slone Survey shows 20-23% of adults

report taking acetaminophen-containing products in the preceding week [2,3,4]. Based on the 2005 US population, there are an estimated 45 million adult users of acetaminophen products in any given week. In 2005, the one-week prevalence of adult use was 17% for aspirin, 16% for ibuprofen, and 4.3% for naproxen [4].

Recently published data from the National Health and Examination Survey (NHANES) and the Nurses Health Survey (NHS) also address trends in adult use of OTC and prescription analgesics. However, the findings of these surveys may not necessarily reflect current medication use trends since nearly all of the data was not recently collected: NHANES III - 1988 to 1994, NHS II –1997, NHS I – 1998, and NHANES - 1999 to 2000 [5,6 7].

8.4.1 Consumer Usage Patterns and Awareness of Acetaminophen

Recently available information shows that the overwhelming majority of consumers report taking acetaminophen at the labeled OTC doses [8,9]. However, as with any product, acetaminophen products can be misused either intentionally or inadvertently.

In order to better understand utilization patterns of OTC acetaminophen-containing products and prescription acetaminophen-combination products, McNeil requested that the Slone Epidemiology Center conduct supplemental analyses of data from the Slone Survey. These supplemental analyses were conducted using data collected from February 1998 to August 2001 and from January 2004 to December 2005 [8,9].

Table 8-1. Slone Analgesic Use Analyses of Data Collected 1998-2001 versus 2004-2005 - Average Daily Acetaminophen Exposure (mg) by Type of Acetaminophen Product Taken By Total of 1378 Adult Users (1998-2001) [8] and 1100 Adult Users (2004-2005) [9]

	- - - - - % Of Product Category Taking Dose Within the Stated Range - - - - -									
	Use of One Product Only						Use of Two Products			
Daily Acetaminophen Exposure (mg)	OTC Single-ingredient		OTC Combination		Rx[b]		OTC Single-ingredient plus OTC combination		Rx[b] plus OTC Single-ingredient products	
	1998-2001 (n=720)	2004-2005 (n=558)	1998-2001 (n=405)	2004-2005 (n=298)	1998-2001 (n=158)	2004-2005 (n=163)	1998-2001 (n=65)	2004-2005 (n=51)	1998-2001 (n=30)	2004-2005 (n=17)
≤2000	72%	71%	85%	81%	43%	55%	37%	41%	27%	29%
2001 to 4000[a]	4%	7%	3%	2%	6%	6%	14%	14%	23%	18%
>4000	0.1%	0.2%[d]	0%	0%	1.6%	0%	8%	0%	3%	6%[c]
4001 to 6000	0.1%	0.2%[d]	0%	0%	1%	0%	5%	0%	0%	n/a
6001 to 8000	0%	0%	0%	0%	0%	0%	3%	0%	3%	n/a
More than 8000	0%	0%	0%	0%	0.6%	0%	0%	0%	0%	n/a
Unknown dose	24%	22%	12%	18%	49%	40%	42%[c]	45%	47%	47%

(n=) Total number of users within the specified category
a: Maximum recommended daily OTC analgesic dose
b: Prescription (Rx) acetaminophen-combination products
c: One subject reported using more than 4000 mg daily (actual dose not specified)
d: This represents one subject who reported using an average daily dose of 4500 mg

Table 8-1 provides a summary of the reported average daily acetaminophen exposure by type of OTC or prescription (Rx) acetaminophen product taken by consumers in these surveys.

Both the 1998-2001 and 2004-2005 Slone Survey data show that of those reporting use of only one acetaminophen product (OTC or Rx), virtually all reported taking less than the maximum labeled dose of 4000 mg/day. In each of the surveys, of those who reported dose and use of only one product, only one individual reported taking average daily doses of more than 4000 mg of an OTC acetaminophen single-ingredient product. The dose reported by this individual in the 2004-2005 Sloan Survey was 4500 mg. Of those who reported use of one product in the 2004-2005 Sloan Survey, no one reported a dose greater than 4500 mg/day with an OTC acetaminophen single-ingredient product.

The highest percentages of unknown acetaminophen doses were from users who reported using prescription acetaminophen-combination products (regardless of whether one or more than one product was used) and from users who reported using more than one OTC

product. From the 2004-2005 data, the most frequently (73%) cited reason for an unknown dose among all acetaminophen users (OTC and Rx) was “unknown dose per pill”.

8.4.2 Prescription Acetaminophen-Combination Product Container Labeling

FDA has identified the following as reasons for unintentional overdose in adults, “the failure of prescription container labels to list acetaminophen as an ingredient” and “container labeling for prescription products, dispensed by a pharmacy, that may not clearly identify acetaminophen as one of the active ingredients and the maximum daily acetaminophen dose limit.” [10, 11].

In FDA’s proposed rule, FDA also cites data involving prescription acetaminophen-combination products. In an FDA analysis of reports of hepatotoxicity coincident with acetaminophen use from the adverse event reporting system (AERS), 33% of adult cases involved the use of a narcotic-acetaminophen prescription product. Approximately 25% of all adult cases reported use of more than one acetaminophen product, with a narcotic-acetaminophen prescription product in combination with an OTC product containing acetaminophen being used more often than any other combination of acetaminophen products [12].

McNeil conducted a survey of 128 adult consumers who had a prescription bottle for an acetaminophen-combination product in their house [13]. Sixty-five percent of people surveyed (83/128) reported the name “APAP” appeared on their prescription container. However, only 12% of these participants (10/83) were able to identify “APAP” as an abbreviation for “acetaminophen”.

All 128 participants from the survey were then provided with a list of warnings and asked to indicate which warnings appeared on their prescription bottle. The data for warnings related to exceeding the recommended dose of acetaminophen are presented in Table 8-2.

Table 8-2 Percentages Of Survey Participants Indicating That A Particular Warning Appeared On Their Prescription Acetaminophen-Combination Product Bottle [13]

Acetaminophen Warning	All Participants (N=128) n (%)
Taking more acetaminophen than recommended can cause serious liver problems.	33 (26)
This medicine contains acetaminophen	19 (15)
Do not take other acetaminophen containing products at the same time without first checking with your doctor	14 (11)

In summary, the McNeil survey results indicate that 1.) the majority of consumers surveyed had prescription acetaminophen-combination container labels that contained the abbreviation, "APAP", 2.) the majority were unable to accurately identify that the abbreviation "APAP" stood for "acetaminophen" and 3.) label warnings about taking more than the recommended dose and taking with other acetaminophen products were reported at best by 37% of participants as appearing on their prescription acetaminophen-combination product bottle.

8.4.3 Unintentional Medication Exposures in Young Children

The Centers for Disease Control and Prevention (CDC) reported that during 2001-2003 children aged 1 year to 2 years had the highest rates of unintended medication exposure. Exposures to OTC medicines (42.2%) were slightly more common than those to prescription medications (39.2%). The most common medicines were acetaminophen, cardiovascular agents, cold and cough products (including combinations), nonsteroidal anti-inflammatory medicines, dermatologic agents, antihistamines, antidepressants, and vitamins. The most common sources of medication exposure were pills left out or pill bottles left open (5.9%), medications administered in error (3.5%), and children opening pill boxes (2.7%) or purses (3.0%) [14]. McNeil has educated caregivers about the importance of keeping medicine out of the reach of children.

8.5 McNeil's Acetaminophen 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 has voluntarily revised its OTC acetaminophen-containing product labeling to direct the attention and enhance awareness of consumers to key label information that may reduce the occurrence of excessive acetaminophen exposure. In addition, McNeil has worked with in-pharmacy prescription label producers to revise labeling on all prescription acetaminophen-combination products. These efforts are described below.

8.5.1 McNeil's Voluntary Labeling Changes for OTC Single-Ingredient and Combination Products

Prior to and since FDA's 2002 NDAC meeting, McNeil voluntarily implemented statements on the labeling of its pediatric and adult Tylenol acetaminophen products that are similar to those now proposed by FDA. These changes included the following:

Pediatric and adult Tylenol products

- Added "Do not use with other products containing acetaminophen" in the warnings section
- Added "Taking more than the recommended dose (overdose) may cause serious health consequences" in the overdose warning; subsequently changed "serious health consequences" to "liver damage".
- Increased prominence of "acetaminophen" on the front of the OTC carton
- Added "Do not take more than directed (see overdose warning)" in the directions

Adult Tylenol products only

- Added "Do not use this adult product in children under 12 years of age; this will provide more than the recommended dose (overdose) and may cause liver damage" in the directions section.

Pediatric Concentrated Tylenol Infants' Drops only

- Changed the name of the products from "Infants' Tylenol Concentrated Drops" to "Concentrated Tylenol Infants' Drops"
- Added "Use ONLY enclosed dropper" on the front of the OTC carton
- Added "IMPORTANT: Concentrated Tylenol Infants' Drops contains more medicine per drop than Children's Tylenol Liquid" to side panel
- Added "Use enclosed dropper ONLY" to side panel
- Added "DO NOT USE other cups or spoons" to side panel

8.5.2 McNeil's Initiative to Improve Container Labeling for Prescription Acetaminophen-Combination Products

In 2002, McNeil sought to revise the labeling information provided on prescription acetaminophen-combination products. McNeil consulted with First Data Bank, one of the major companies that provided drug label database services to most of the pharmacy market. McNeil advised them of the importance of improving labeling on all prescription acetaminophen-combination products. First Data Bank then independently created and added to their labeling database the following two new auxiliary warning labels (ie, those labels placed directly on prescription bottles) specific to acetaminophen, which may be included on the prescription containers at the discretion of the pharmacist:

- 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 you Doctor. Check all medicine labels carefully.

An additional revision to the database was implemented that replaced abbreviations, such as “APAP”, with the word “acetaminophen”.

Based on the survey results mentioned in Section 8.4.2 and the AERS cases described in Section 8.4.2, McNeil recognizes that there is further opportunity to improve prescription acetaminophen-combination product container labeling to increase consumer awareness of ingredients in these products. FDA is silent in this rulemaking about supporting possible actions to improve labeling for prescription acetaminophen-combination products. McNeil encourages FDA to address this public health concern through prescription product and professional labeling initiatives. McNeil encourages FDA, Pharmacy and Medical Associations, and other interested stakeholders to work to improve container labels of prescription acetaminophen-combination products, to increase consumer understanding that prescription acetaminophen-combination products contain the active ingredient “acetaminophen”, and to improve the education of healthcare professionals on these matters.

8.6 McNeil’s Educational Initiatives

While the vast majority of consumers use OTC acetaminophen according to labeled directions, McNeil recognizes that some consumers may exceed the maximum labeled dose. McNeil is committed to encouraging the proper use of its medicines and has a long history of implementing educational initiatives encouraging the appropriate use of its products.

8.6.1 McNeil Focuses its Educational Initiatives on Consumer Analgesic Behaviors

Since 2002, McNeil has implemented educational initiatives designed to help minimize intentional or inadvertent consumer misuse of OTC analgesics that may result in excessive analgesic exposure. McNeil focuses these educational initiatives on the following four consumer analgesic use behaviors:

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

- When using prescription acetaminophen-combination products 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.
- 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, thus taking increased doses of some ingredients.
- When using pediatric products – caregivers may not adhere to or access proper dosing directions and may not properly store medications.

These four consumer analgesic use behaviors are based on findings from a McNeil Survey [15] of adult consumers in the US who had used OTC analgesics in the past six months, as well as the FDA 2002 NDAC meeting regarding OTC pain relievers and an FDA 2004 Science Background Paper [10], based on the safety data presented at the 2002 NDAC meeting.

8.6.2 McNeil's Educational Initiatives Targeting Consumers

8.6.2.1 National Council on Patient Information and Education (NCPIE) "Be MedWise" Campaign

In 2002, McNeil provided an educational grant to the National Council on Patient Information and Education (NCPIE) to fund the nationwide "Be MedWise" program, a multi-media effort to increase public awareness of OTC product ingredients and their uses. The program included television and print advertisements, and an Internet web site (www.bemedwise.org). Many of the materials were developed in cooperation with the FDA. For example, NCPIE produced a television advertisement aimed at encouraging consumers to avoid the use of two or more medications that each contained the same active ingredient. The ad reached 70% of the US population. It featured 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 communication points included:

- "Know What's in Your Medicine" - designed to encourage consumers to read medication labels and 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 presented on the label.

Impact of "Be MedWise" Campaign

The National Council on Patient Information and Education (NCPIE) conducted two national surveys to track the opinions of consumers and health professionals about the use of OTC medicines. The first survey, conducted during October and November of 2001, consisted of 1011 adults 18 years of age and older [16]. A second NCPIE survey of 1009 adults was conducted during May and June of 2003 to determine the impact of NCPIE's "Be MedWise" educational campaign about the use of OTC medications [17]. The 2003 survey was conducted a year after the OTC Drug Facts label was required for most OTC drug products. Findings include:

- In 2003, 44% of consumers reported that they consult the OTC product label for the active ingredient– up from 34% in the previous 2001 NCPIE survey.
- In 2003, 20% of consumers surveyed reported reading the label for possible side effects compared to only 10% who looked for this information in 2001.
- There was an increase in the number of consumers who reported reading the label for dosage instructions – 16% of consumers in 2001 compared to 23% of consumers in the 2003 survey.

Among the 2001 NCPIE survey respondents who were asked about taking more than the recommended dose of a nonprescription medicine, 33% recalled ever taking more than the recommended dose in belief that it would increase the effectiveness of the product. In the 2003 NCPIE survey, 48% of consumers stated that they have taken more than the recommended dose of a nonprescription medication, believing that it will increase the effectiveness of the product and 51% of respondents reported taking an OTC medicine and a prescription medicine, both of which contained the same active ingredient, simultaneously.

8.6.2.2 McNeil's "Know Your Medicine" campaign

In 2002, McNeil launched its "Know Your Medicine" campaign to complement the NCPIE "Be MedWise" campaign. This initiative sought 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

McNeil delivered these key messages included through print and radio advertising, direct mail, retail outlets, the Internet, and healthcare professionals. This campaign was a bilingual, campaign, with messages and educational materials targeting both English- and Spanish-speaking consumers. Key education partners in the McNeil "Know Your Medicine" initiative included the American Academy of Family Physicians (AAFP) and the American Pharmacist Association (APhA).

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

- Distribution of over 11 million "Know Your Medicine" consumer education brochures.
- Partnerships with major pharmacy chains resulting in distribution of retailer-branded brochures that incorporated the "Know Your Medicine" message (eg, CVS, Target, Walgreens, and Wal-Mart).
- Collaboration with healthcare professionals to distribute tip cards, brochures, and patient education tear pads with "Know Your Medicine" messages.

8.6.2.3 McNeil's "Responsible Use of Medicine" Education Campaign

In 2004, McNeil launched its "Responsible Use of Medicine" campaign targeting adults and caregivers of children, as well as healthcare professionals. This initiative encourages proper dosing and awareness of Tylenol acetaminophen products using key messages:

- Take the recommended dose of Tylenol
- Taking too much of any medication can cause serious problems, no matter how safe it is
- Read and follow the label
- Keep medicine out of the reach of children
- Use the appropriate pediatric dosing device
- Pediatric Tylenol acetaminophen products have different concentrations

Delivery of these key messages includes print and television advertising, the Internet, and through healthcare professionals. The campaign included two television commercials and one print advertisement targeting adult consumers; visual frames and the full script of each advertisement are shown below in Figures 8.2, 8.3, and 8.4. Together, these 3 advertisements were viewed approximately 2.114 billion times from 2004-2006.

Figure 8.2 Script and frame from television commercial targeting adult consumers, directing them to "read the label".

Script: Chances are you've seen what I work on, but you may not have read it. I help make sure the instructions on your Tylenol package are correct. Over-the-counter medicine is strong medicine and it needs to be taken correctly. You have to read the label. Taking care of consumers is really important to me. It's an important part of my job. If you're not going to take the time to read the label and take Tylenol properly, we'd rather you didn't take it at all.
Text: Stop. Think. Tylenol.com

Figure 8.3 Script and frame from television commercial targeting adult consumers, directing them to not take Tylenol if they are "not going to take the recommended dose".

Script: Some people think if you have a really bad headache, you should take extra medicine. Problem is, that's not going to get rid of your headache faster. And taking too much of any medication, no matter how safe it is can cause serious problems. Your health is important to us, so if you're not going to take the recommended dose of our medicine, I'd rather you just didn't take it. And if that means selling less Tylenol, that's fine with me.
Text: Stop. Think. Tylenol.com

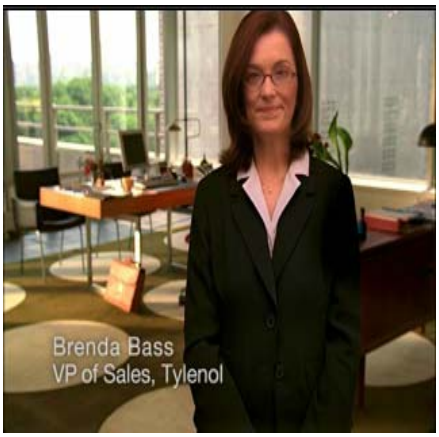


Figure 8.4: Print advertisement targeting adult consumers to "read the label, and take only the recommended dose".

Text: If you don't take the recommended dose of Tylenol, we recommend you don't take it at all. We take your health seriously and we want you to take our medicine the same way. Please be sure to read the label, and take only the recommended dose. Because while Tylenol is safe when used as directed, it's also strong. And taking too much of any medication can cause serious problems. Stop. Think. Tylenol.com

The campaign also included four print advertisements and 2 online Web Banner advertisements targeting caregivers of children, one shown below in Figure 8.5. From 2004-2006, the 4 print advertisements were viewed 183 million times and in 2006, the Web Banners were viewed 255 million times.

Figure 8.5: Print advertisement targeting caregivers of children

Text: Our Infants' Medicine Isn't Half As Concentrated As Our Children's. It's Three Times More Concentrated. Because it's more difficult to get medicine into an infant's mouth, we've made our infants' medicine more concentrated. Which means if you give it to toddlers, you could be giving them too much. That's why we have created products designed for your children's specific age and weight, so follow the instructions and use only the dosing device provided. Responsible dosing. It's one more step towards a pain-free world. Stop. Think. Tylenol.com

Finally, multiple consumer education tools were made available on Tylenol.com, including:

- What You Should Know About Liver Health
- Pain Relievers Explained: Test Your Knowledge
- Pain Relievers Explained: How to Read a **Drug Facts** Label
- Pain Relievers Explained: Medicine Packaging and Child Safety
- Keeping Medicines Out of Reach
- Not Reading the Labels of OTC Medicine Can Be Dangerous
- Pain Relievers Explained: Children's Dosage Guide with Downloadable Fever Diary
- What Every Parent Should Know About Children's Medications With Downloadable Medication Record
- Infants' Dosing Tips With Downloadable Dosing Facts And Reminders

Together, these tools were accessed or downloaded 336,485 times during 2005-2006.

Impact of "Responsible Use of Medicine" Education Campaign on Consumer Attitudes

Prior to launch of the "Responsible Use of Medicine" campaign, McNeil sought to understand the impact of the campaign's key messages on consumer attitudes related to the appropriate use of Tylenol. McNeil conducted consumer research testing of the print advertisement shown in Figure 8.4 [18]. Compared to a control group who did not view the advertisement, the consumers who viewed the print ad were significantly more likely to indicate that they think its important to pay attention to the recommended dosing on the label of non-prescription pain relievers (44% vs. 33%, significant at 95% confidence level).

Following the launch of the national campaign, McNeil sought to measure the campaign's impact on consumer attitudes towards acetaminophen. In-market testing of the two television advertisements (Figures 8.2 and 8.3), which comprised over 80% of this campaign's reach, was conducted through an online survey [19]. Adults who recalled seeing the first television advertisement (Figure 8.2) were significantly more likely to answer "yes, I think there are side effects associated with acetaminophen" to the question, "Do you think that acetaminophen medications (for example: Tylenol Extra Strength, Tylenol 8 Hour) will cause any damage to your body from side effects?" compared to adults who did not recall seeing the television advertisement (41% vs. 33%, significant at the 95% confidence level). Additionally, those who recalled seeing the television advertisement were significantly more likely to indicate "liver damage" as a potential side effect of

acetaminophen, compared to participants who did not recall seeing the television advertisement (34% vs. 28%, significant at the 95% confidence level).

Adults who recalled seeing the second television advertisement (Figure 8.3) were significantly more likely to answer "yes, I think there are side effects associated with acetaminophen" to the question, "Do you think that acetaminophen medications (for example: Tylenol Extra Strength, Tylenol 8 Hour) will cause any damage to your body from side effects?" compared to adults who did not recall seeing the television advertisement (39% vs. 30%, significant at the 95% confidence level). Additionally, those who recalled seeing the television advertisement were significantly more likely to select "liver damage" as a potential side effect of acetaminophen, compared to participants who did not recall seeing the television advertisement (31% vs. 26%, significant at the 95% confidence level).

Based on this research, the "Responsible Use of Medicine" campaign is creating greater consumer awareness of potential risks that may be associated with the improper use of acetaminophen.

8.6.2.4 McNeil's Partnership with Retailers to Provide Education Accompanying Prescription Acetaminophen-Combination Products

McNeil has recently implemented a pilot program with ten ShopRite Pharmacies in the Northeast. When the pharmacist processes a prescription for an acetaminophen-combination product, a patient-directed educational brochure is automatically printed. The pharmacist may then provide this brochure to the patient when they pick up their prescription. The key messages in the educational brochures include the following:

- This medicine contains acetaminophen.
- Acetaminophen is also a medicine in many over-the-counter pain relievers and cold/flu products such as Tylenol or Tylenol Cold.
- Do not take this medicine with these or any other acetaminophen-containing products because you can easily exceed the recommended dose.
- Taking more than the recommended dose of acetaminophen may cause liver damage.

McNeil plans to expand this program into other retail pharmacies to provide this educational tool more broadly.

8.6.3 McNeil's Educational Initiatives Targeting Healthcare Professionals

McNeil initiatives include efforts to educate physicians, pharmacists, and other healthcare professionals and provide tools intended to help reduce the occurrence of inappropriate OTC analgesic use.

- McNeil continues to provide dosing information for pediatric Tylenol and Motrin products through *Physician's Desk Reference*, physician offices and pharmacies.
- In March 2007, McNeil distributed "Responsible Use of Medicine" kits to 53,000 primary care offices. These kits contained patient education brochures that listed OTC products that contain acetaminophen and a wall poster with instructions for how to read a **Drug Facts** label. Additional copies of these materials are made available to physicians upon request.

8.6.4 McNeil's Partnerships with American Academy of Family Physicians (AAFP) and American Pharmacist Association (APhA)

McNeil recognizes the importance of partnering with healthcare professional organizations to increase the effectiveness of educational efforts. McNeil has partnered with AAFP and APhA on several educational initiatives, some of which are described below.

In 2002, McNeil provided an educational grant to AAFP to develop an educational monograph entitled, "Appropriate Use of Common OTC Analgesics and Cough and Cold Medications" 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. More recently, in 2005, McNeil provided an educational grant to develop five consumer education tools that were made available on familydoctor.org, the American Academy of Family Physicians consumer health information website. The education tools were designed to teach consumers about OTC medicines, including knowing what's in OTC medicines, how to read an OTC drug label, and how to administer the correct dose to children.

Additionally, McNeil was a founding sponsor of APhA's American Pharmacists Month, a nationwide campaign aimed at encouraging patient/pharmacist interaction. A key message is that the best way for patients to know their medicine is to know their pharmacist. McNeil also partnered with APhA to develop APhA—T.A.L.K. print brochure, a tool designed to direct consumers to read the label and talk to their pharmacist about their medicines. McNeil was a founding sponsor for the APhA Self-Care Institute, a yearly conference for pharmacy school faculty engaged in self-care instruction.

8.6.5 McNeil's Previous Labeling and Educational Initiatives

McNeil has a long history of developing initiatives to promote the safe and appropriate use of OTC medicines. In addition the extensive education and labeling initiatives described above, prior to 2002, McNeil:

- Initiated the N-acetylcysteine (NAC) IND for the treatment of acetaminophen overdose (1978).
- Funded support for Rocky Mountain Poison Center to answer consumer and healthcare professional questions related to acetaminophen and 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).
- Introduced the SAFE-TY-LOCK system for Infants' Tylenol Suspension Drops to promote proper administration of infants' concentrated acetaminophen drops (1999).
- Filed a Citizen Petition with the FDA to expand dosing directions on OTC pediatric acetaminophen product labeling to include children under two years of age (1999) [20].

8.7 McNeil's Future Initiatives and Recommendations

McNeil remains committed to developing, supporting, and implementing labeling and educational initiatives directed to consumers, caregivers of children, and healthcare professionals, and focusing attention on consumer misuse behaviors involving OTC

acetaminophen-containing products that may contribute to overdose. McNeil encourages FDA, Pharmacy and Medical Associations, and other interested stakeholders to work to improve container labels of prescription acetaminophen-combination products, to increase consumer understanding that prescription acetaminophen-combination products contain the active ingredient “acetaminophen”, and to improve the education of healthcare professionals on these matters. Finally, McNeil passionately urges FDA to respond to McNeil’s outstanding Citizen Petition requesting that the dosing directions on OTC pediatric acetaminophen product labeling be expanded to include dosing for children under 2 years.

8.8 Reference List

1. IMS Health: National Sales Perspectives (NSP) 2001-2006.
2. 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(3):337-344.
3. Slone Epidemiology Center. Patterns of medication use in the United States. Results of a population-based telephone survey. 2004. Available at: www.bu.edu/slone/SloneSurvey/SloneSurvey.htm. Accessed January 5, 2007.
4. Slone Epidemiology Center. Patterns of medication use in the United States. Results of a population-based telephone survey. 2005. Available at : www.bu.edu/slone/SloneSurvey/SloneSurvey.htm. Accessed January 5, 2007.
5. Paulose-Ram R, Hirsch R, Dillon C, et al. Prescription and nonprescription analgesic use among the US adult population: results from the third National Health and Nutrition Examination Survey (NHANES III). Pharmacoepidemiology and Drug Safety 2003;12:315-326.
6. Paulose-Ram R, Hirsch R, Dillon C, et al. Frequent monthly use of selected non-prescription and prescription non-narcotic analgesics among U.S. adults. Pharmacoepidemiology and Drug Safety 2005;14:257-266.
7. Curhan GC, Bullock AJ, Hankinson SE, et al. Frequency of use of acetaminophen, nonsteriodal anti-inflammatory drugs, and aspirin in US women. Pharmacoepidemiology and Drug Safety 2002;11:687-693.
8. Slone Epidemiology Center. Analgesic use in the adult population of the United States: acetaminophen, aspirin, ibuprofen, and naproxen. Results of a population-based telephone survey, 1998-2001. McNeil Consumer Healthcare data on file, October 2001.
9. Slone Epidemiology Center. Analgesic use in the adult population of the United State in 2004-2005: acetaminophen, aspirin, ibuprofen, and naproxen. Results of a population-based telephone survey. McNeil Consumer Healthcare data on file, December 2006.
10. FDA Science Background: Safety Concerns Associated with Over-the Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use. January 22, 2004. Available at: http://www.fda.gov/cder/drug/analgesics/SciencePaper.htm. Accessed May 4, 2007.
11. FDA Letter to State Boards of Pharmacy. Acetaminophen Hepatotoxicity and Nonsteroidal Anti-Inflammatory Drug (NSAID)-related Gastrointestinal and Renal Toxicity. January 22, 2004. Available at: http://www.fda.gov/cder/drug/analgesics/letter.htm. Accessed May 4, 2007
12. 71 FR 77314 at 77320-21

13. McNeil Consumer Healthcare. McNeil Contents of Warning Labels on Prescription Bottles Dispensed with Products Containing Acetaminophen. Data on file, 2007.

14. Centers for Disease Control and Prevention. Nonfatal, unintentional medication exposures among young children—United States, 2001-2003. MMWR 2006;55:1-5.

15. McNeil Consumer Healthcare. McNeil OTC Habits and Practices Study. Data on file, 2001.

16. National Council on Patient Information and Education (NCPIE). Attitudes and beliefs about the use of over-the-counter medicines: A dose of reality. January 2002. Available at: http://www.bemedwise.org/survey/final_survey.pdf. Accessed January 5, 2007.

17. National Council on Patient Information and Education (NCPIE). Uses and attitudes about taking over-the-counter medicines: findings of a 2003 national opinion survey conducted for the National Council on Patient Information and Education. September 2003. Available at: http://www.bemedwise.org/survey/summary_survey_findings.pdf. Accessed January 5, 2007.

18. McNeil Consumer Healthcare. Data on file, 2004.

19. McNeil Consumer Healthcare. Data on file. 2006.

20. McNeil Citizen Petition, Docket Number 77N-0094, Labeling for dosing of acetaminophen in children under age two, Dated 2/1/99, Amended 8/15/2001.