	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
4	Thomas, et al 2000	Compare Feb to Aug 1998 (N=116) and Feb to Aug 1999 (N=112)	UK	Admissions for OD at one hospital	• Number of APAP OD decreased; 52 (45% of all OD)) to 40 (36%) • 30 (68%) took more than 16 tabs before compared to 18 (51%) after legislation • Non-APAP increased; 64 to 72 cases • Time in hospitals same for both periods	Author: may have less liver transplant unit needs, but still need hospital care	"Our results suggest that patients are now switching to alternative agents… there may be less demand for liver units, but the unwanted workload for general physicians is the same." Note: number of other drugs increased
5	Hawton et al, 2001 (see updated study below)	Databases from 1996 to 1999	UK	England and Wales mortality data (Sep 1996 to Sep 1999); liver transplantations and listings from 5 units (Oct 1996 to Sep 1999); non-fatal poisonings presentations at 7 hospitals (Sep 1997 to Sep 1999)	• Decreased numbers of deaths; 21% for APAP and 48% for ASA • Number of liver unit admissions decreased 30% • Number of APAP non-fatal poisonings deceased 11% • Percent OD with >32 tabs decreased 17% • Significant increase in OD with APAP compounds in 4 of the hospitals (Author says maybe b/c of decreased availability of APAP)	Dargan et al: period of study is too short	"Legislation restricting pack sizes of APAP and ASA has had substantial beneficial effects on mortality and morbidity associated with self poisoning using these drugs."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
6	Balit C et al, 2002	Compare Mar to May and Jun to Aug 1997-1999 compared to Mar to May and Jun to Aug 2000; study recall effect	Western Australia	Calls to poison control center and presentations to Toxicology Service	• No significant change in APAP or ASA calls over total recall; but was a non-significant decrease in APAP calls in the first recall period • Saw significant increase in ibuprofen calls and ASA presentations		"Reduced APAP availability increased poisonings for alternative analgesics, but had little effect on the incidence APAP poisonings."
7	Hughes et al, 2003	Apr 1995 to Jan 2003	UK	Admissions to two hospitals with APAP OD (1 hospital) and number admitted to liver unit (1 hospital)	• 31% decrease in number of patients admitted to hospital (average 360 to 250 per year) • 50% decrease in admission to liver units (average 76 to 38 per year)	Author: decrease in liver unit admissions may be due to staffing shortages. May also see decrease in pediatric deaths	"Legislation restricting APAP pack-size reduced the incidence and severity of poisoning."
8	Kisely et al 2003	1996 to 2001: Australian recall Mar 16 to May 21, 2000 (146 days)	Western Australia	Poisoning admission rate in WA; use WA population for denominator and time series analysis	• Significant decrease in admission rate (p=0.01) • Also decrease for ibuprofen or ASA or other drugs; all rates decreased. • Weekly time series analysis found non significant decrease in APAP admissions	Author: admissions for APAP OD showed large random variation that tended to obscure any effect	"Limiting access to APAP may reduce APAP poisonings without an coincident increase in the use of other agents."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
9	Hawton et al, 2004	Databases from 1993 to 2002	UK	England and Wales mortality data (1993 to 2001); liver transplantations and listings from all but 1 unit in England and Scotland (1996 to 2002); non-fatal poisonings presentations at 5 hospitals (1997 to 2001)	• Deaths (suicide, open verdicts and accidental) for any APAP or ASA decreased 22% • 30% decrease in admission to liver units for APAP OD and also 30% decrease for transplants • 15% decrease in APAP presentations to hospitals in first year but not after; number of ibuprofen increased by 27% in 2nd and 3rd year but mortality was not greatly affected (11 to 13 deaths) and other drugs were involved. • OD > 32 tabs decreased significantly in years 2 and 3 for APAP and ASA, not ibuprofen		"Legislation restricting pack sizes of analgesics has been beneficial." Note: Ibuprofen OD increased, but with little effect on death.
10	Prior, et al 2004	Apr 1995 to Mar 2001; follows lifting of place-of-sale restrictions on APAP that allowed the sale of all strengths of IR APAP (had been limit of >325 mg and all packages of	Canada	Canadian hospital discharge data	• Compared rates (used population as denominator) and found no significant change • **Of note** the rates were consistently higher for the provinces that never had an acetaminophen restriction policy regardless of time period.	Author comments that may be too early to analyze.	"The decision to lift Canadian place-of-sale restrictions increased APAP availability and did not increase the rate of reported hospitalizations related to APAP OD."

	Study	Year	Location	Outcome	Findings	Comments	Author's Summary
		>24 tablets)					
11	Bateman, et al 2004	1995 to 2004	Scotland	In-hospital deaths (1995 to 2004) and hospital discharges (1995 to 2003) for Scotland	• Majority of deaths were due to co-proxamol • Proportion of deaths related to APAP was higher after legislation • Overall the number of poisonings fell post legislation but those involving APAP in any form decreased for <20 years and increased for those over 20 years		"Legislations have not reduced mortality or proportional use of APAP in OD, both of which appear to have increased in Scotland since pack-size limitations."

Department Of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation

Nonprescription Drug Clinical Review

Acetaminophen-Induced Hepatotoxicity

Subject	Acetaminophen-induced hepatotoxicity
Active Ingredients	Acetaminophen (APAP)
Indication	Temporary relief of minor aches and pains and temporary reduction of fever
Target Population	Individuals ages six months and older
Dosage/Route of Administration	Children less than 12 years of age: 10 – 15 mg/kg Individuals 12 years and older: 650-1000 mg Q4-6 hrs up to 4 g/day
Review Completion Date	March 8, 2007
Review Content	Data on acetaminophen-induced hepatotoxicity from 2002 – 2006 Regulatory and educational options to mitigate this risk
Reviewers	Karen B. Feibus, M.D. Steven Osborne, M.D.

Table of Contents **Page**

Introduction

Data from a large national survey suggest that 36% of Americans ingest an acetaminophen-containing compound at least once a month.[1] Compared with the millions of acetaminophen tablets consumed by Americans each day, the incidence of acute liver failure (ALF) due to acetaminophen is low. However, use of twice the recommended daily dose for a few days causes severe liver failure and death in some individuals. Acetaminophen (APAP) has been the number one cause of drug-induced liver failure in children and adults since at least the 1990's[2], but in 2005, APAP became the number one cause of acute liver failure in the United States.[3] The purposes of this paper are to:

- Review the published data on acetaminophen-associated hepatotoxicity in adults and children from 2002 to 2006
- Present regulatory and educational options that may reduce the unintentional (and possibly intentional) overuse and abuse of acetaminophen-containing products that can lead to hepatotoxicity and its associated morbidity and mortality.

Intentional overdose with APAP has a well-characterized risk of hepatotoxicity, liver failure, and possible death. The International Classification of Diseases categorizes acetaminophen overdose as "clearly intentional acetaminophen overdose" with intent of suicide or self-inflicted injury and as "not clearly intentional acetaminophen overdose", which apparently includes any other cause of acetaminophen overdose. During the past decade, recognition and concern about APAP-associated hepatotoxicity associated with acute or chronic overdosing with therapeutic intent has grown. Pediatric and adult patients with unintentional APAP overdose pose a greater diagnostic challenge, as they often develop symptoms subtly over a longer period of time and present with more advanced hepatotoxicity than those with an acute intentional overdose. Either acute or chronic unintentional overdose may include multiple APAP-containing drugs, increasing the risk of hepatotoxicity. Kearns et al. commented that *acetaminophen overdose with therapeutic intent constitutes a toxicologic entity distinct from acute intoxication in both its presentation and epidemiology*.[4] However, the literature does not specify whether an acetaminophen overdose due to deliberate ingestion of more than the recommended dose, with therapeutic intent, should be classified as an intentional or unintentional overdose. For this review, unintentional overdose refers to accidental poisoning and any overdose in which suicide or self-inflicted injury was not the goal.

Acetaminophen: Regulatory History

In 1960, FDA approved a new drug application for the over-the-counter (OTC) marketing of a 325 mg immediate-release tablet formulation of APAP for the following indications:

> *The temporary relief of minor aches and pain associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever.*

On July 22, 1975, FDA approved NDA 17-552 for Extra Strength Tylenol 500 mg APAP immediate release tablet with a maximum daily dose of 4 g. Superior efficacy of the 1000 mg

dose of APAP versus the 650 mg dose of APAP was supported by two clinical studies in women with post-episiotomy pain.

As part of the OTC Drug Review process, the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Products recommended APAP as a Category I analgesic product and expressed concerns about the public not regarding OTC products as medicines that can *result in injury or potentially serious consequences* and stated that the public needs to know that all medicines carry some risk and should be treated with respect (42FR35346, ANPR 07/08/1977). The Panel recommended that all products containing acetaminophen contain the following liver warning: *Do not exceed recommended dosage because severe liver damage may occur (42FR35355).*

A Proposed Rule (PR) for Internal Analgesic Products published on November 16, 1988 (53FR46204). After review of many comments that opposed organ-specific label warnings on analgesic products, FDA decided to omit the Panel's recommended liver warning for acetaminophen from the PR. However, FDA acknowledged that it was appropriate to warn consumers of potential drug toxicities associated with use of an OTC drug and that it may be necessary to include organ-specific warnings.

Table 1 displays the current indications and durations for use for nonprescription acetaminophen-containing products as described in the 1988 PR.

Table 1: OTC Acetaminophen Indications and Durations for Use

Population	Indications	Duration of Use
Adult (12 years and older)	For the temporary relief of minor aches and pains associated with the common cold, sore throat, headache, toothache, muscular aches, backache, premenstrual and menstrual cramps, the minor pain from arthritis, and to reduce fever	3 days for fever 10 days for pain
Children (2 years to under 12 years of age)	For the temporary relief of minor aches and pains associated with the common cold, sore throat, headache, toothache, and to reduce fever	3 days for fever 5 days for pain

The PR included a dosing range based upon age, but did not include dosing for children younger than age two years or dosing based on weight. However, as found in the 2007 Physician's Desk Reference (PDR) for Nonprescription Drugs, Dietary Supplements, and Herbs, acetaminophen is currently marketed with dosing that includes children younger than two years of age and dosing by weight[75]. Thus, Tables 2 and 3 display dosing schemes for currently-marketed adult and pediatric acetaminophen products[75].

Table 2: Dosing for APAP Non-chewable Tablets		
Product	**Age**	**Dose**
APAP 325 mg	Under 6 years	Do not use
	6 to 11 years	1 tablet every 4 to 6 hours as needed. Do not take more than 5 doses in 24 hours.
	12 years and older	2 tablets every 4 to 6 hours as needed. Do not take more than 12 tablets in 24 hours, or as directed by a doctor.
APAP 500 mg	Under 12 years	Do not use
	12 years and older	2 tablets every 4 to 6 hours as needed. Do not take more than 8 tablets in 24 hours, or as directed by a doctor.

Table 3: Dosing for APAP Concentrated Infant Drops and Children's Suspensions*			
Product	**Weight**	**Age**	**Dose**
APAP Concentrated Infant Drops (80 mg/0.8 mL)	6 to 11 pounds	0-3 months	½ dropperful (40 mg)
	12 to 17 pounds	4 to 11 months	1 dropperful (80 mg)
	18 to 23 pounds	12 to 23 months	1 ½ dropperfuls (120 mg)
	24 to 35 pounds	2 to 3 years	2 dropperfuls (160 mg)
APAP Children's Liquids	Under 12 pounds	Under 4 months	Consult a doctor
	12 to 17 pounds	4 to 11 months	½ teaspoon (80 mg)
	18 to 23 pounds	12 to 23 months	¾ teaspoon (120 mg)
	24 to 35 pounds	2 to 3 years	1 teaspoon (160 mg)
	36 to 47 pounds	4 to 5 years	1 ½ teaspoons (240 mg)
	48 to 59 pounds	6 to 8 years	2 teaspoons (320 mg)
	60 to 71 pounds	9 to 10 years	2 ½ teaspoons (400 mg)
	72 to 95 pounds	11 years	3 teaspoons (480 mg)

*manufacturer says to use weight if possible; otherwise use age. Also, take no more than 5 doses in 24 hours.

In September 2002, the Nonprescription Drugs Advisory Committee (NDAC) and members of the Office of Drug Safety (ODS, now the Office of Surveillance and Epidemiology, OSE) addressed unintentional overdose of acetaminophen and hepatotoxicity. FDA stated that acetaminophen should remain available OTC given its overall effectiveness and safety, the benefits that an OTC pain reliever/fever reducer offers to consumers, and its use by tens of millions of people each week. FDA noted factors that contribute to unintentional overdose and acetaminophen-associated hepatotoxicity:

- Acetaminophen is available to consumers in many OTC and prescription drug products
- Consumers fail to identify acetaminophen as an ingredient in their OTC and prescription drug products
- Consumers are not aware of the risks of exceeding the recommended dose or dosing frequency of acetaminophen-containing products or the risks of simultaneously using multiple acetaminophen-containing products.

Following discussion of data presented by FDA, industry, researchers, and the public, NDAC made the following recommendations:

- All products containing acetaminophen should be distinctively labeled (highlighted or bold) on the front panel or principle display panel with the name acetaminophen.
- On the OTC products, the committee recommended a liver toxicity warning separate from the currently required alcohol warning.[5]
- FDA and manufacturers should educate consumers and health professionals about the risk associated with ingesting too much acetaminophen and the occurrence of unintentional liver injury.
- The committee agreed with including dosing directions in children's products for children < 2 years of age.

Following the AC meeting, FDA Consumer Magazine summarized the advisory committee's recommendations in their January 2003 issue and presented information on unintentional acetaminophen-induced hepatotoxicity and non-steroidal anti-inflammatory drug-related gastrointestinal bleeding. FDA launched a consumer campaign on the safe use of OTC pain products in January 2004. This program included printed public service announcements (PSAs), a FDA Science Paper posted on the internet, and a letter sent to all fifty State Boards of Pharmacy that stressed the importance of clear-labeling of acetaminophen content on all dispensed prescription medicines containing acetaminophen. Based on advisory committee recommendations, the Division of Over-the-Counter Drug Products (now the Office of Nonprescription Products, ONP) drafted a proposed rule requiring an organ specific liver warning and a size-specified, prominent appearance of the word "acetaminophen" on the principal display panel for all acetaminophen-containing nonprescription drug products. This document was published on December 26, 2006.

On December 4-5, 2006, the National Institutes of Health (NIH) hosted a meeting on Acute Liver Failure. The objectives of the meeting were to convene experts on and assess current knowledge about acute liver failure: its causes, incidence, natural history, management, and prevention. A portion of the meeting focused on APAP hepatotoxicity. Relevant, but as yet unpublished, information shared at the meeting is integrated into this options paper where appropriate.

Acetaminophen: Mechanism for Hepatotoxicity and Concomitant Risk Factors

The mechanisms of APAP toxicity and concomitant risk factors that may predispose to toxicity are presented in Appendix A at the end of this paper.

Acetaminophen-Induced Hepatotoxicity in Adults

Although intentional APAP overdose has been a public health problem and a recognized cause of liver failure in the United Kingdom since the 1970's, APAP was not mentioned as a cause of acute liver failure (ALF) in the United States until the 1980's. A U.S. retrospective study from 1994-1996 found that 20% of ALF cases are caused by acetaminophen toxicity. The majority of reports involve intentional APAP overdose, but cases of APAP-associated hepatotoxicity from unintentional overuse for treatment of pain and hepatic injury following therapeutic doses also appeared in the literature.

In preparation for the September 2002 AC, FDA reviewers from the Office of Drug Safety reviewed APAP-associated hepatotoxicity data from national databases and the FDA Adverse Event Reporting System (AERS) to estimate the public health impact of hepatotoxicity in the United States. This information is presented below. This data is followed by summaries of published studies from 2002 – 2006, including the first two studies published by the U.S. Acute Liver Failure Study Group (US ALFSG). In 1997, this consortium of liver centers formed to better define the causes and outcomes of ALF and to compare presenting clinical features and liver transplantation rates between patients with ALF related to APAP overdose and those with ALF due to other drugs, causes, or indeterminate factors.

FDA Summary of Population Database Information on Acetaminophen-Associated Hepatotoxicity (1990 – 2001)

Drs. Nourjah, Ahmad, Karwoski, and Willy, reviewers from CDER's OSE, published a study presenting national estimates of APAP-associated overdoses obtained by analyzing national databases.[6] The authors used six different surveillance systems that included data from emergency departments (EDs), hospital discharges, mortality data, poison control centers, and spontaneous postmarketing adverse drug event reports reported to the Food and Drug Administration (FDA). Among the six surveillance systems listed below, the first three are national surveys that use probability sampling. Additional details about these information sources may be found in Appendix B.

- National Hospital Ambulatory Medical Care Survey (NHAMCS)
- Consumer Product Safety Commission's National Electronic Injury Surveillance System All Injury Program (NEISS)
- National Hospital Discharge Survey (NHDS).
- National Multiple Cause of Death File (mortality files)
- Toxic Exposure Surveillance System (TESS)
- FDA Adverse Event Reporting System (AERS)

Findings from this study were presented and discussed at the September 2002 NDAC and are summarized in the Key Data Points window below. A detailed review of Nourjah et al's 2006 publication is provided in Appendix B.

Key Data Points
56,000 Emergency department visits and 26,000 hospitalizations per year for APAP associated overdose – 63-69% female.
About 458 deaths per year (in 1990's) caused by or contributed to by APAP – 58% female.
Unintentional overdose probably accounts for about 25% of cases (8% NHDS, 22% Cause of death files, 23% ED data, 26% TESS, 41% AERS)
Most APAP overdoses involve the use of one APAP product but 10 – 26% involved the use of two or more products, often an OTC and a RX product.
Toxicity, including death, occurred with mean daily doses less than twice the maximum recommended daily APAP dose of 4 g/day. Up to 30% of individuals with APAP toxicity reported to AERS took 4g/day or less.

Comment:
FDA AERS database crude counts for acetaminophen-associated deaths in 2004, 2005, and 2006 suggest that cases of acetaminophen-associated hepatotoxicity and death are not declining. However, these data should be viewed with caution since multiple drugs may have been listed as associated with the death and the role of acetaminophen may be unclear.

Other Published Data on Acetaminophen-Associated Hepatotoxicity in Adults

Gyamlani and Parikh (2002)
When Gyamlani and Parikh[7] published their February 2002 study report on APAP toxicity, APAP was the second leading cause of toxic drug ingestion in the United States (it is now the first). Their objective was to describe the epidemiology of various types of APAP poisoning and analyze their outcomes in an urban county hospital (East Meadow, NY). The authors identified all admission records from January 1996 – April 1999 with a discharge diagnosis of APAP overdose. Patients evaluated or treated in the emergency room, who were not admitted to the hospital, were excluded from the study. The authors reviewed the medical records and confirmed APAP ingestion by history (self or family), blood level (> 10 mg/L), or serum aminotransferase level > 1000 IU/L. Patients had to meet two out of these three criteria for inclusion. Chronic alcohol abuse was defined by the DSM- IV[8] criteria.

Reviewer comment:

1. *It is not clear whether the authors chose an APAP serum level of > 10 mg/L because this was the lower limit of detection for their laboratory or if they chose it for another reason.*

2. *The Rumack-Matthew nomogram estimates that a serum APAP level of 10 mg/L is possibly or probably toxic if the APAP was ingested more than 19 hours prior to the serum measurement (from Acetadote® Injection labeling approved 02/14/2006).*

3. *In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV),* ***alcohol abuse*** *is defined as a maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested in a 12-month period by one or more of the following problems: (1) failure to fulfill role obligations at work, school, or home; (2)*

recurrent use of alcohol in hazardous situations; (3) legal problems related to alcohol; and (4) continued use despite alcohol-related social problems.[9]

The authors identified one hundred eligible patients but excluded seven due to co-morbid conditions or clinical presentations unrelated to acetaminophen ingestion. APAP ingestion accounted for 7.5% of all hospital poisoning admissions during this time. Among the 93 eligible subjects, eighty (86%) were classified as suicidal based on psychiatric evaluation, and 13 (14%) were classified as accidental (unintentional) overdoses while seeking to relieve pain. Causes of pain included toothache, chronic backache, and headache. Mean peak serum APAP levels were higher in patients with intentional overdose (122 mg/L vs. 65 mg/L), but a greater percentage of patients with unintentional overdose had peak aminotransferase levels greater than 1000 IU/L (39% vs. 12%). Morbidity and mortality were higher in the unintentional overdose group. Two patients with unintentional APAP overdose developed ALF, hepatic coma, and died. One of these patients had a history of chronic alcohol abuse.

Patients with unintentional overdose ranged in age from 1 – 88 years with a median of 36 years (mean 35 years). Five of these patients were female and 10 were Caucasian. Five (38%) patients met the DSM-IV criteria for chronic alcohol abuse, and three (23%) were intoxicated at the time of presentation. By comparison, 18% of suicidal patients with acetaminophen overdose met the DSM-IV criteria for chronic alcohol abuse and 45% were intoxicated upon arrival at the hospital. Some patients in the unintentional overdose group were unaware that their over-the-counter drugs contained acetaminophen. Thirty-eight percent of patients with unintentional overdose had APAP levels less than 10 mg/L. These subjects met the other two study criteria for APAP overdose: substantial APAP ingestion by history and serum aminotransferase level > 1000 IU/L. The authors attributed the subjects' low APAP serum levels to late presentation and ingestion of smaller APAP doses over a longer period of time compared to their suicidal counterparts.

The authors noted that peak plasma APAP levels are unreliable in predicting hepatic dysfunction, especially in patients with accidental overdose. They recommended that patients with unintentional overdose should be considered for N-acetylcysteine treatment and that chronic alcohol abusers should be treated at APAP plasma levels half of those indicated in the standard graph. In addition, the authors noted that 75 of 80 patients with suicidal overdose and all 13 patients with unintentional overdose were admitted to the intensive care unit for one to two days at a cost of $25,000 – 35,000 per day (in 1999).

Ostapowicz et al, US ALFSG (2002)
Larson et al, US ALFSG (2005)

In December 2002, Ostapowicz et al[10] and the US Acute Liver Failure Study Group (ALFSG) published data on their first 308 patients with ALF. Hepatic coma was graded on a standard scale of I to IV. At each study center, etiologic diagnoses were based on accepted diagnostic criteria circulated to all investigators. These criteria incorporated: history, laboratory values, imaging studies, and histopathology characteristics in some cases. The cause of ALF was indeterminate when extensive clinical, radiographic, and laboratory evaluation (including toxicology screens and serologic markers for viral hepatitis A, B, and C and antinuclear and anti-smooth muscle antibodies) was inconclusive. Investigators used RNA testing methods to search

for other viral etiologies when clinically indicated, but results were not uniformly available. Clinical guidelines for patient management were uniform even though they were determined at each study site. Candidacy for liver transplantation was determined at each individual medical center according to the guidelines of the United Network of Organ Sharing.

Seventy-three percent of the subjects were female, and the etiologies for ALF were as follows: 39% APAP overdose, 13% idiosyncratic drug reactions, 7% Hepatitis B, 4% Hepatitis A, and 2% pregnancy associated liver failure (acute fatty liver, HEELP syndrome, eclampsia). Forty-two subjects had presumptive diagnoses of ischemic hepatitis, autoimmune hepatitis, Wilson's disease, and Budd-Chiari syndrome. Among subjects with APAP-associated ALF, 83% used more than the maximum daily recommended APAP dose of 4 g/day, but 17% used a daily APAP dose of 4 g or less. Half of the subjects with APAP-associated ALF overdosed accidentally.

This study was ongoing, and in 2005, Larson et al[11] reported on the subpopulation of 275 subjects with acetaminophen-associated ALF among 662 US ALFSG patients who enrolled between January 1, 1998, and December 31, 2003.

Demographic, clinical, laboratory, and outcome information were prospectively recorded for all subject meeting study entry criteria for ALF at the 22 participating academic centers. By definition, eligible subjects met the following criteria:

- INR ≥ 1.5
- Evidence of hepatic encephalopathy
- Presented within 26 weeks of illness onset without apparent chronic liver disease
- Written informed consent by legal next of kin.

Whenever possible, study staff obtained the following information on each patient's APAP ingestion: total dose, type of acetaminophen product used, and duration of use. To assign APAP ingestion as the cause of acute liver failure (ALF), a patient had to meet one or more of these criteria:

- History of potentially toxic APAP ingestion (> 4g/day) within seven days of presentation
- Detection of any serum level of APAP
- Serum alanine aminotransferase (ALT) > 1000 IU/L and a history of APAP ingestion.

In addition, study staff had to exclude other potential causes of ALF such as acute hepatitis A or B, hepatic ischemia, autoimmune hepatitis, Wilson disease, and hepatitis of other etiologies. The local site investigators assigned patients with APAP-related ALF to one of two groups:

- Intentional (suicidal) ingestion: a single time-point ingestion in a patient admitting suicidal intent
- Unintentional ingestion: a multiple time-point ingestion to relieve pain or other somatic symptoms with denial of suicidal intent.

The study defined alcohol abuse in terms of daily alcohol consumption: at least 40 g/day for men and at least 20 g/day for women.

Reviewer comments:

- *A standard drink in the United States contains 14 g ethanol. A standard drink in the United Kingdom and Australia contains 10 g ethanol. There are 42 g of ethanol in 3 standard U.S. drinks. There are 21 g of ethanol in 1.5 U.S. drinks.*[12]

- *Among subjects who used alcohol but did not meet the study definition for alcohol abuse, the authors did not distinguish between acute and chronic alcohol use or identify non-daily abuse (binging).*

Each center applied its own liver transplantation criteria to study patients admitted to that center. Study investigators reviewed all case report forms at the central study site (University of Texas, Southwestern Medical Center) to confirm subject diagnoses.

Among 662 ALF subjects enrolled in the study, 302 (46%) had APAP-related hepatotoxicity. On further review, the investigators excluded 27 of these subjects because there were insufficient data to rule out other causes or because co-existing clinical conditions may have contributed to the ALF (like viral hepatitis, poly-drug use, or shock). During each year of the study, acetaminophen was the most common cause of ALF and this percentage increased annually from 28% in 1998 to 51% in 2003. Idiosyncratic drug-induced hepatotoxicity was the second most common cause (12%) and the cause was indeterminate in 19% of subjects.

The final study group with APAP-associated hepatotoxicity included 275 subjects (42% of the 662 ALF subjects enrolled in the study). Seventy-four percent were female and this percentage was consistent among those with intentional and unintentional overdose. Subjects with APAP-related hepatotoxicity ranged in age from 17 to 76 years and in weight from normal to morbidly obese. Median body mass index (of 196 calculated) was in the normal range. The vast majority of subjects were Caucasian (88%) with African Americans comprising 5% of the study population. Hispanics, Asians, Native Americans, and other races each made up two percent or less of the population. One hundred fifty-five (56%) subjects met all three criteria for assigning APAP ingestion as the cause of ALF. Serum APAP levels were detectable in 212 (77%) subjects, and ALT was ≥ 1000 IU/L in 250 (91%) subjects.

Data Summary Points
662 cases of acute liver failure
275 cases APAP-associated
204 (74%) female
242 (88%) Caucasian
122 (44%) intentional overdose
131 (48%) unintentional overdose

(N=275 unless otherwise stated)
182 (66%) used an OTC APAP product
147 used only OTC APAP products
-141 (96%) used 1 OTC product
- 6 (4%) used 2 OTC products
120 (44%) used a Rx narcotic/APAP
- 76 (63%) used narcotic/APAP alone
- 41 (34%) used narcotic/APAP+OTC
47 (17%) used > 1 APAP product

151 (55%) used alcohol (N=273)
68 (35%) abused alcohol (n=196)
108 (39%) used an anti-depressant

79 (29%) died

Table 4 summarizes available clinical information about the study population as a whole and by overdose intent. One hundred twenty-two (44%) subjects reported an intentional overdose and 131 (48%) experienced an unintentional overdose without suicide intent. Intent was not clear in 8% of subjects. Compared to those attempting suicide, subjects with unintentional overdose were, on the whole, older (median 38 vs. 34 years), more likely to use multiple APAP-containing preparations (38% vs. 5%), and more likely to seek care longer after symptom onset (median 4 days vs. 1 day). These subjects were more likely to have severe hepatic encephalopathy (grades 3 or 4) at

Table 4: Features and Outcomes for Subjects With Acetaminophen-Related ALF (all measures of central tendency are medians)

Characteristic		All [N = 275]	Unintentional Overdose* [N = 131]	Intentional Overdose* [N = 122]
Age in years (age range)		37 (17-76)	38 (18-76)	34 (17-68)
Female gender (%)		204 (74%)	96 (73%)	90 (74%)
Body Mass Index (Normal = 19-25 kg/m^2)		-	25 (17-51) [N=97]	24 (16-56) [N=99]
Serum APAP level, µg/dL [N]		31 (0-644) [N=257]	18 (0-400) [N=119]	64 (0-644) [N=118]
APAP dose, g	Median Daily (range) [N]	-	7.5 (1.0-7.8) [N=77]	25 (1.2-90) [N=91]
	Median Total (range) [N]	-	20 (2.5-180) [N=81]	25 (1.2-90) [N=91]
Alcohol use		151 (55%) [N=273]	-	-
Alcohol abuse		68 (35%) [N=96]	-	-
OTC APAP product	1 product 2 products	141 (51%) 6 (2%)	-	-
APAP/narcotic product	Total Alone With OTC APAP	120 (44%)** 76 (28%) 41 (15%)	83 (63%)	22 (18%)
Anti-depressant use		108 (61%)	48 (37%)	46 (38%)
INR (Normal = 0.8-1.2)	Median (range) N(%) ≥ 3.0	3.0 (1.2-27.1)	56 (42%)	68 (56%)
Bilirubin, mg/dL	Median (range) N(%) ≥ 4	4.5 (0.3-48.2)	73 (56%)	74 (61%)
Serum ALT, IU/L	Median (range) N(%) ≥ 3500	4186 (136-19,826)	3319 (126-18,079) 63 (48%)	5326 (179-19,826) 88 (72%)
Serum creatinine	Median mg/dL (range) N(%) ≥ 2 mg/dL	2.0 (0.2-10.5)	74 (57%)	53 (43%)
Peak Hepatic Coma Stage 3 or 4		-	89 (68%)	72 (59%)
Hepatic coma grade on admission	1 2 3 or 4	84 (31%) 52 (19%) 135 (50%)	- - 72 (55%)	- - 47 (39%)
Liver Transplantation	Listed Received Days to Transplant	- - -	35 (27%) 12 (9%) 3 (1-7)	30 (25%) 8 (7%) 3 (2-5)
Overall outcome	Survived, no transplant Died, no transplant Transplant, lived 3 weeks Died, post-transplant	178 (65%) 74 (26%) 18 6%) 5 (2%)	84 (64%) - - -	80 (66%) - - -
Overall survival at 3 weeks		181 of 253 (72%)	94 (72%)	87 (71%)

*Type of overdose not known in 22 (8%) subjects.

** APAP/narcotic alone vs. with OTC APAP were unknown for 3 subjects.

admission but lower serum APAP levels than their suicidal counterparts. There were no other clinically significant differences between the two subject groups. Educational level was similar for the two groups and averaged 13.22 years for the population as a whole.

One hundred forty-one (51%) ALF subjects used one OTC APAP product alone, and six (2%) used two OTC APAP products. Among the 120 subjects who used a combination APAP/narcotic product, 76 (63%) subjects used the prescription product alone, and 41 (34%) used it in combination with an OTC APAP product. In total, concomitant use of more than one APAP-containing product contributed to liver toxicity in 47 (17%) subjects. Among users of APAP/narcotic combination products, 63% experienced unintentional APAP overdose and 18% reported an intentional overdose. The authors did not specify how many individuals using OTC APAP products alone experienced an unintentional versus an intentional overdose. All data shown is from the publication.

Information on alcohol use was available for 273 subjects of whom 55% used alcohol chronically (see comment after Table 4). Among the 196 subjects for whom actual alcohol intake was recorded, 35% met the criteria for alcohol abuse. Compared with non-abusers, alcohol abusers had lower APAP levels (median 15 µg/dL vs.34 µg/dL), were less likely to use anti-depressants (24% vs. 40%) or compound narcotics (31% vs. 50%, see comment below)), and were less likely to present with severe hepatic encephalopathy (34% vs. 53%). Seventy-seven subjects had toxicology screen results available, and 58 were positive. Half of these positive results were for illicit drugs (marijuana, cocaine, and amphetamines), and half were positive for potential drugs of abuse thought to represent prescribed medications (opiates, benzodiazepines, barbiturates, tricyclic antidepressants).

Comments:

- *The authors do not define chronic alcohol use or distinguish it from occasional use.*

- *It is important to remember that the definition of alcohol abuse for this study is three standard U.S. drinks per day for a male and 1.5 standard drinks per day for a female. Most people in American society do not consider this amount of alcohol intake to constitute abuse. This study suggests that the alcohol warning on APAP labeling should reflect a gender difference.*

- *The authors use the term "compound narcotics" in the paragraph above. This term apparently refers to a combination narcotic-acetaminophen product.*

Sixty-one percent of subjects used at least one anti-depressant, and anti-depressant use occurred with equal frequency among subjects with unintentional and intentional APAP overdose. Individuals using anti-depressants were, on average, older (median 39 yrs) and more likely to use prescription APAP/narcotic combination products (55% vs. 37%) and more likely to use additional prescription narcotics (17% vs. 5%).

Nineteen (7%) subjects reported taking 4 g of APAP per day or less prior to presentation: 14 experienced an unintentional overdose; 16 had ALT levels greater than 1000 IU/L; and 12 had measurable APAP serum levels. Seventy-nine percent of these individuals used alcohol and 65% with alcohol consumption data met the criteria for alcohol abuse. For comparison, subjects who

consumed more than 4 g/day APAP had a 37% prevalence of alcohol abuse. This difference was statistically significant.

Among those with unintentional overdose, 81% reported a cause of pain for which they used the APAP-containing drug. These reports included: chronic pain, chronic back pain, headache, chronic abdominal pain, viral upper respiratory infection, migraine, toothache, orthopedic pain, fibromyalgia, rheumatologic pain, chronic pancreatitis, and postsurgical pain. Nineteen (15%) of 131 subjects with unintentional overdose reported using acetaminophen for more than seven consecutive days. This group differed from subjects using acetaminophen for fewer than seven days in the following ways: older, greater weight, more likely to report pain as the reason for drug use, more likely to use additional narcotics, less likely to use alcohol.

Among 72 (26%) subjects listed for liver transplantation, 20 died, 29 recovered without transplant, and 23 (8%) underwent transplantation. Seventy-nine (29%) subjects died within three weeks of admission: 74 without transplantation and five following transplantation. Seventy-two percent of subjects with unintentional overdose and 71% of subjects with intentional overdose survived until three weeks post-admission. Individuals who used APAP chronically and those who acutely ingested an overdose exhibited the same type of acute liver injury and clinical presentation.

The authors noted the recent increase in the percentage of acute liver failure cases associated with APAP use and estimated that at least 250 APAP -related ALF cases and 73 deaths occur annually at transplant centers in the United States. This number does not account for APAP-related hepatotoxicity cases cared for at non-transplant centers and is less than the 458 APAP-related deaths per year predicted by FDA's Office of Drug Safety in 2002 based on an adverse event data review. Fifty percent of individuals developed hepatotoxicity and encephalopathy from unintentional overdose. The authors identified the following factors as potential contributors to unintentional APAP overdose scenarios:

- Repeated dosing in excess of package labeling
- Use of multiple acetaminophen-containing products
- Simultaneous use or abuse of alcohol and narcotics
- Chronic pain conditions
- Depression.

The authors suggest that drug regulatory changes in the United States may be needed to reduce the incidence of APAP-induced hepatotoxicity (limiting OTC package size, physically separating the narcotic and APAP components of combination prescription products, education for healthcare providers and consumers).

The authors noted the following strengths and limitations of their study. Strengths included representation of 30% of the U.S. transplant capability, evaluation of all subjects by experienced hepatologists, and inclusion of only the 60% of cases with informed consent and adequate data to ensure the diagnosis. The authors acknowledged that the study population may not represent the true incidence of ALF in the population as a whole since many patients are not referred to

transplant centers. In addition, medical history taking is difficult in patients with altered mentation.

Editorial comments published in response to the two US ALFSG articles described the eligibility criteria and definitions of APAP-associated hepatotoxicity as subjective and inaccurate respectively.[13] The comments raised concerns about whether subjects who consumed ≤ 4 g/day APAP really had APAP-associated hepatotoxicity.[14] A series of questions regarding the study data prompted a detailed response from William Lee, US ALFSG member that published in July 2004. Dr. Lee acknowledged that figures from the ALSFG studies on APAP-associated hepatotoxicity could not be equated with actual incidence figures; however, the documented increase in the percentage of ALF cases attributable to acetaminophen is striking. In addition, he noted that there is a difference between all patients entering the hospital with presumed APAP overdose and the small percentage of them who develop ALF. The US ALFSG only admits patients who develop coagulopathy and encephalopathy. For comparison, Parkland Memorial Hospital admitted 71 APAP overdose patients in a 39-month period but only seven patients developed acute hepatic failure and died. One patient died among the fifty who were considered suicidal, whereas six patients died among 21 with unintentional overdoses. [15] In his July 2004 publication, Dr. Lee also noted the recent development of an assay that reliably detects acetaminophen-containing protein adducts released into the plasma by dying hepatocytes. The assay allowed confirmation of unrecognized acetaminophen toxicity in 20% of ALF patients previously classified with liver failure of undetermined etiology. In the Ostapowicz study, 20% of patients with established viral hepatitis had detectable APAP serum levels. Compared to viral hepatitis patients without detectable APAP levels, these patients had significantly higher median ALT levels (5400 IU/L vs. 1367 IU/L). Although these patients were not considered APAP-associated ALF cases in the study, the use of APAP in the presence of chronic hepatitis may have contributed to the patients' acute morbidity.

Reviewer comment:

- *At the December 4, 2006, NIH Acute Liver Failure workshop, Laura James, M.D. presented unpublished data from her laboratory and the U.S. ALFSG showing that serum protein adducts strongly correlate with elevations of hepatic transaminases and are detectable in serum up to 10 days following severe APAP overdose. She also stated that recent modifications in the high-performance liquid chromatography-electron capture assay increased the sensitivity and efficiency of the test.*[16]

- *Unpublished data addressing APAP protein adducts in ALF patients with hepatitis are discussed in the next reviewer comment.*

Two editorial comments published in response to the Larson et al article raised concerns about the definition of cases of unintentional APAP overdose. Holubek et al stated that the exclusion criteria did not specifically include Hepatitis C, hepatotoxic drug exposure, or viral etiologies. Also, any person accompanying the patient could have provided a history of a multiple time-point APAP ingestion to relieve pain or other somatic symptoms with denial of suicidal intent. They felt that this presented a large recall and selection bias.[17] John G. O'Grady acknowledged that Larson et al adopted a broader set of diagnostic criteria for APAP-related hepatotoxicity and stated that only 40% of the patients fulfilled a more conventional definition of having a clear

history of taking APAP in excess, having detectable APAP serum levels, and having markedly raised transaminases. While these broader criteria almost *certainly resulted in the inclusion of some cases that were not truly related to acetaminophen use*, he felt that the credibility of the study results were supported by the remarkable similarity between the typical patients with acknowledged overdoses and the group whose disease was attributed to the therapeutic use of misuse of APAP. Other than having a median age six years older, the two groups were very similar with regards to demographics, natural history, and outcome.[18]

O'Grady suggested that the diagnostic criteria for APAP-related hepatotoxicity should be loosened and that the burden of proof for establishing the diagnosis should be lower than that used in the past. Although Larson et al concluded that ALF patients with a history of therapeutic use of APAP reach a point where they become acutely susceptible to liver injury (rather than representing a variant of acetaminophen liver injury with a more protracted pathogenesis), O'Grady states that that possibility of dual pathology in these patients should be considered given the likelihood that APAP will be used therapeutically in patients with viral illnesses. APAP is a significant co-factor in the pathogenesis of ALF in patients with acute Hepatitis B and those using anti-tuberculosis drugs.

Reviewer comment:

- *At the December 4, 2006, NIH Acute Liver Failure workshop, Julie Polson, M.D. presented unpublished data on protein adducts in hepatitis patients. The protein adduct assay conducted in Dr. James' lab detected acetaminophen adducts in sera from more than 12% of ALFSG patients with acute liver failure confirmed to have hepatitis A or B. Most of these patients reported using APAP at recommended doses to treat their symptoms of fever, myalgias, arthralgias, and headache. Hepatitis patients with positive adducts had 67% mortality at three weeks compared to 27% mortality in those without adducts. Dr. Polson stated that adduct levels in hepatitis patients were lower than those seen in patients with primary APAP-induced ALF but still suggest that ingestion of APAP likely contributed to liver injury.*[19]

While the work of the US ALFSG provides the most extensive and prospective data on APAP-associated ALF in the United States, data from Australia offers some similar findings regarding the occurrence of unintentional acetaminophen overdose. Unlike the United Kingdom where the vast majority of APAP overdoses are believed to represent suicide attempts or gestures, researchers from Australia have identified cases of unintentional acetaminophen overdoses that resemble those in the United States.

Gow et al (2004)

Gow et al[20] published a database review in 2004 that included patients 16 years and older who were referred to the one transplant center in Melbourne between 1988 and 2001. Among 80 patients (80% female) referred to the transplant center for ALF, 29 (36%) had APAP poisoning and 24 (83%) were female. Nine of the 29 patients had an unintentional overdose, and all of these accidental overdoses involved taking regular APAP over a period of several days for the treatment of pair or febrile illness. The authors reviewed the case histories for these patients and found that all nine had poor dietary intake during the period of APAP ingestion, and five had a history of long-term, excessive alcohol intake. Patients with APAP-associated ALF were listed

for transplantation only if they developed coagulopathy or cerebral edema (encephalopathy). The authors estimated that the rate of referral to the Victorian Liver Transplant Unit was about one case per million population per year but did not provide comparisons to other liver transplant centers in Australia. Consistent with data from the United States and the United Kingdom, the authors found that the vast majority of patients with APAP-induced ALF survived without transplantation. They did not provide data about amount of APAP ingested and did not differentiate outcomes for patients with intentional and unintentional overdose.

Reviewer comment:

- *The data from Gow et al (2004) and the data from Larson et al (2005) suggest that ALF due to intentional and unintentional APAP overdose is more common in women. At the December 4-5, 2006, NIH workshop on Acute Liver Failure, Anne Larson, M.D. stated that the U.S. ALFSG patient data were analyzed by body mass index to look for an association between body mass, gender, and outcome. No association was found. It should be noted, however, that the ALFSG study population is limited to individuals with ALF and encephalopathy. In order to determine whether smaller body mass contributes to a greater number of APAP-associated ALF cases among women than men, multiple comparisons should be considered:*
  - *Differences in number of males and females using APAP products*
  - *Differences in use patterns among males and females*
  - *Differences in BMI among female APAP users with acute or chronic overdose/overuse who do and do not develop ALF.*

Ayonrinde et al (2005)

In 2005, Ayonrinde et al[21] published a retrospective observational study of patients with APAP overdose admitted between January 2000 and December 2003 to a regional hospital in Victoria Australia. The authors reviewed the medical records of 188 of 192 patients who presented to the hospital after an APAP overdose. Patients were excluded if they consumed less than 2 g APAP by history or if paracetamol levels were undetectable. The authors classified nine cases as unintentional overdoses. These individuals used APAP for analgesia to treat toothache, back pain, or abdominal pain and consumed quantities of APAP similar to those consumed intentionally by other patients. No cases of hepatotoxicity resulted from a therapeutic dose of APAP. Twenty-six (14%) of patients with APAP overdose developed elevated ALT, four developed coagulopathy, and one developed encephalopathy, and six (3%) developed severe hepatotoxicity. The authors do not state how many patients with unintentional overdose developed hepatic injury, and American data suggest that individuals with unintentional overdose often have a more severe clinical course than those with intentional overdose.

Reviewer comment:

- *The authors did not specifically define "unintentional overdose." International Classification of Diseases -10 codes were used to identify patients with APAP overdose. Codes utilized included: intentional self-harm; analgesics, antipyretics and antirheumatics; poisoning by non-opioid analgesics, antipyretics, and antirheumatics; accidental poisoning by and exposure to noxious substances; and event of undetermined intent.*

Watkins et al (2006)
In this study, Watkins et al[22] demonstrated that some normal healthy volunteers who used APAP 1000 mg Q6 hours either alone or in combination with oxycodone, hydromorphone, or morphine sulfate for 14 days developed elevated liver transaminases. The authors conducted this study after they stopped a drug development trial early due to a high incidence of ALT elevations in subjects receiving the combination APAP/hydrocodone product under development. Subjects received four grams APAP per day. One hundred forty-seven healthy men and women, ages 18 – 45 years participated in this randomized, single-blind, placebo-controlled, parallel-arm, two-center study. Each subject was randomized to one of five study treatments in a 1:1:1:1:1.5 ratio:

- 2 tablets Percocet (7.5 mg oxycodone/500 mg APAP) + 2 tablets placebo
- 2 tablets Dilaudid (2 mg hydromorphone0 + 2 tablets 500 mg APAP
- 2 tablets 15 mg morphine sulfate + 2 tablets 500 mg APAP
- 2 placebo tablets + 2 tablets 500 mg APAP
- 2 placebo tablets + 2 placebo tablets

Subjects were housed in a clinical facility for the duration of study participation and received their study treatment every six hours for up to 14 days. Among subjects receiving placebo, 3% had ALT levels that reached two times the upper limit of normal, and no subjects had levels that reached three times the upper limit of normal. Among subjects in the four active treatment arms, 19% had ALT levels that reached five times the upper limit of normal. When peak ALT elevations were normalized by baseline values, 3% of placebo users had a peak ALT level more than five times their baseline value but 27% of active treatment subjects had a peak ALT level more than eight times their baseline value. There were no meaningful differences in the magnitude or incidence of elevated ALT among subjects in the different active treatment arms; however, there was a statistically significant difference between the placebo treated group and all of the active treatment groups with regard to ALT elevations. Exposure to any APAP was the single best predictor of elevated ALT response. All subjects remained asymptomatic.

Except for one subject in the morphine group and one in the APAP alone group who were lost to follow-up on Study Day 19, the abnormal ALT values remained elevated for a few days following cessation of treatment and then rapidly fell back into the normal range. Compared to non-Hispanic Americans, Hispanic Americans were nearly twice as likely to have a maximum ALT more than three times the upper limit of normal (RR = 1.9, 95% CI 1.1 – 3.3). There were no differences in mean APAP troughs, peak concentrations, or AUCs between subjects with and without ALT elevations. The researchers concluded that the opioids did not appear to contribute to the ALT elevations see among subjects in the active treatment groups as there were no significant differences in the frequency or magnitude of ALT elevation among subjects who took APAP alone and those who took it in combination with an opiate.

Bolesta and Haber (2002)
In 2002, Bolesta and Haber[23] published a literature review that evaluated the potential for APAP to cause toxicity in adult patients without risk factors who used 4 g/day or less chronically. Individuals who took more than 4 g/day APAP, who used APAP for less than four days, or who were less than 18 years of age were excluded. The authors identified four case reports that met these criteria, and these cases are summarized in Table 5.

Table 5: Four cases of acetaminophen-induced hepatotoxicity in adults without risk factors			
Age (yrs)/Gender	**Indication for use/ Medical History**	**Dose/Duration**	**Outcomes**
59 F	Arthritis	2.925 g/day for 1 year	Increased AST Liver enzymes normalized after discontinuation of APAP. Rechallenge resulted in elevated AST.
53 M	Chronic hip and shoulder pain Infectious hepatitis 25 years earlier	3.9 g/day for 13 months	Hepatomegaly, increased AST AST normalized with discontinuation but elevated again with two rechallenges.
25 M	Enrolled in study where subjects received warfarin and APAP	APAP: 1 g QID for 21 days Coumadin; 20 mg on Days 2 and 16.	On Day 18 of APAP, AST and ALT were above normal. APAP was stopped and ALT an AST levels returned to normal baseline levels in two weeks.
67 M	Chest pain, History of heart failure, angina, myocardial infarction One congenital kidney	1 – 3 g/day for 2 – 4 days Other medicines: Furosemide, persantine, captopril, doxycycline.	AST, ALT, total bilirubin, BUN, serum creatinine were elevated on admission. Levels rose for the first few days after admission and then declined. Normal levels after 2.5 months. Serum APAP levels were in the normal range. Patient was treated with N-acetylcysteine.

The authors concluded that patients can develop hepatotoxicity from chronic APAP therapy at recommended doses despite a lack of risk factors for toxicity. They pointed out that such cases may be underreported due to a lack of clinical suspicion of acetaminophen toxicity.

Acetaminophen-Induced Hepatotoxicity in Children

The problem of APAP-related hepatotoxicity is not confined to adults. APAP accumulation in pediatric patients after repeated doses was described over two decades ago by Nahata et al.[24] Although acute liver failure can be a dramatic clinical syndrome, a high index of suspicion is necessary is necessary to diagnose APAP-related hepatotoxicity in very young children. Symptoms are initially nonspecific and may mimic the disorder for which the product was administered, such as a febrile illness in a child with accompanying malaise, anorexia and nausea. Diagnoses can be further complicated in the young child with limited communication ability.

Acetaminophen is the most widely used analgesic and antipyretic in infants and young children worldwide.[25] Pediatric acetaminophen formulations include concentrated drops, liquids, chewable tablets, and meltaways. The recommended maximum daily dose of APAP is 75 mg/kg in children (versus 4 g in adults). Losek et al note that in children from newborn to 11 years, the manufacturer's recommended dose is 7.4 to 14.8 mg/kg/dose, no more than 5 times in 24 hours, which yields 37 to 74 mg/kg/day.[26] Therefore, dosages over 15 mg/kg administered more often than 5 times in 24 hours (>75 mg/kg) result in supra-therapeutic dosing of APAP. Nahata et al estimate the minimum single dose capable of producing liver toxicity at 150 mg/kg in children[23],

while Muniz et al estimate single doses exceeding 200-250 mg/kg may be toxic.[27] The current OTC pediatric dosing for APAP was presented in Table 3. Dosage is based on weight and age.

Reviewer comment:

- *On December 18, 2002, the Division of Over-the-Counter Drug Products (now ONP) completed a Health Hazard Evaluation on a children's APAP product. At that time, there were 17 published cases of severe liver damage reported following multiple dosing of APAP at a total daily dose of ≤ 100 mg/kg. An October 2001 review from the Office of Drug Risk Assessment (now OSE) noted that 11 of 117 children developed severe liver injury after receiving more than 75 mg/kg/day and less than 100 mg/kg/day APAP. Three of these children died.*

FDA Office of Surveillance and Epidemiology Reviews on Acetaminophen Overdose and Hepatotoxicity in Children

Between 2001 and 2002, OSE completed three reviews examining post-marketing reporting data and published literature on acetaminophen overdose and hepatotoxicity in children.

Consult for ONP: Pediatric Adverse Events With Use of APAP (2001)

In 2001, OSE reviewer Carol Holquist completed an internal consult from the Division of Over-the-Counter Drug Products (now the Office of Nonprescription Products) on adverse events associated with use of APAP in the pediatric population. The review included data on APAP from several sources including:

- Sponsor reports to FDA for adverse drug experiences and consumer inquiries for all McNeil *pediatric dosage forms* for the time period 1/1/92-8/31/00

- Sponsor reports to FDA for adverse drug experiences covering misadministration of *adult acetaminophen dosage forms to children* less than 12 years of age for the time period 1/1/92-8/31/00

- Sponsor reports to FDA for reports made to two Poison Control Centers (National Capital Poison Control Center and the Utah Poison Control Center) for *children 0-11 years of age* for the time period 1/1/00-12/31/00.

For all McNeil pediatric dosage forms for the time period 1/1/92-8/31/00, 973 reports were identified using the following COSTART terms: accidental overdose, intentional overdose, and overdose. The search identified 973 relevant reports, and 117 were cases of drug misadministration. Eighty-six of the 117 cases of drug misadministration involved use of various pediatric formulations of acetaminophen while the remaining 31 cases involved unspecified acetaminophen formulations or products. The majority of reports involved use of the 500 mg Extra Strength Tylenol product (65%) mostly by children between 6 and 11 years of age. Table 6 (next page) shows the distribution of these adverse event reports by age and Tylenol product.

Table 6. Post-marketing reports of APAP overdose in children by age and Tylenol product

Age Range	Junior Strength Tylenol (n=3)	Child. Tylenol Chew Tabs (n=17)	Unk APAP Syrup or Elixir (n=3)	Child. Tylenol Susp. or Elixir (n=14)	Infant's Tylenol Concen. Drops (n=50)	Unk APAP Suppository (n=1)	Unk APAP Product (n=9)	Unk Tylenol Product (n=5)	Unk Paracet. Product (n=14)	Panadol (n=1)
0-2 mo.	0	0	0	0	4	0	0	0	0	0
>2-6 mo.	0	0	0	1	8	0	1	0	0	0
>6 mo. – ≤2 yr.	2	1	1	6	32	0	5	2	5	0
>2 yr. - ≤6 yr.	0	11	2	3	2	1	1	1	8	1
>6 yr. - <12 yr.	1	5	0	2	1	0	2	0	1	0
>12 yr.	0	0	0	1	0	0	0	0	0	0
Unknown	0	0	0	1	3	0	0	2	0	0

McNeil submitted a total of 54 case reports involving misadministration of adult APAP dosage forms to children less than 12 years of age. Twelve of these reports were coded as *accidental overdose* or *overdose*, but 35 cases were not coded as overdose but still represented misuse of the adult formulation. One case involved use of an unknown brand of acetaminophen suppository, and six cases involved use of a paracetamol (foreign-marketed APAP) product. Thirty-five reports involved use of Extra Strength Tylenol (65%) and the majority of these involved children six to 11 years of age. Seventeen cases involved some type of hepatic involvement, five of which resulted in death and three in liver transplants. Although the majority of total case reports involved the Extra Strength APAP formulation, the majority of serious injuries occurred in patients who either self-administered or were prescribed an inappropriate dose or utilized an inappropriate dosing interval for the Regular Strength formulation (6). All but one report described multiple dosing of an APAP product. The most common indications for use were fever, URI symptoms, teething, and stomach cramps.

Sponsor-submitted data from two Poison Control Centers (National Capital Poison Control Center and the Utah Poison Control Center) included 1730 cases of APAP exposure in children 0-11 years of age for the year 2000. Of these 1730 cases, 544 (31%) involved APAP maladministration. There were no cases of moderate or major effect or death. Adverse events experienced with APAP combination products appeared to be related to the antihistamine, decongestant, or opioid component of the product. The most common types of errors reported were:

- Incorrect doses secondary to not reading and/or misinterpreting the directions for use of product
- Inadvertent duplicate administrations by parents /caregivers
- Concomitant administration of two acetaminophen-containing formulations
- Administration of the wrong formulation and/or concentration based on the patient's age/weight.

In summary, the majority of calls to the two Poison Control Centers involved single-ingredient APAP pediatric formulations. The specific products most frequently reported in medication error cases were Infant Tylenol Concentrated Drops and Children's Tylenol Suspension or Elixer.

OSE Review of two published case series on APAP-related hepatotoxicity (2002)
In 2002, OSE reviewer, Syed Ahmad reviewed two published case series on APAP-related hepatotoxicity in children and adolescents ages five weeks to 19 years. In 1997, Rivera-Penera et al. reported 73 pediatric cases of APAP-induced hepatotoxicity. The amount of APAP ingested was 77-608 mg/kg/day. Twenty-eight (38%) children had abnormal liver tests at baseline, and of these, six children underwent liver transplantation and one died. The remaining 22 children received conservative management – 21 recovered and one died. Forty-five children with normal liver tests at baseline recovered with conservative management. In 1998, Heubi et al. reported 47 pediatric cases of APAP-induced hepatotoxicity. The amount of APAP ingested was 60 – 420 mg/kg/day, and 24 (52%) of the children received adult APAP formulations. Twenty-four (52%) children died, and three survived with liver transplantation. The reviewer concluded that the following factors contribute to acetaminophen-related liver toxicity in children:

- Miscalculations in dosing by parents and caregivers
- Simultaneous administration of multiple products without the knowledge of parents/caregivers that these products contain APAP
- Administration of adult strength products
- Delayed therapy
- Concomitant ingestion of other hepatotoxic drugs.

Reviewer comments:

- *Rivera-Penera noted that one parent used a teaspoon instead of the dropper for the infant solution (80 mg/0.8 ml), and another used the adult regular-strength tablets (325 mg) instead of the chewable children's tablets (160 mg). They concluded that parental misguidance in dosing children 10 years of age and younger, and "suicide gestures" by children 11 years of age and older, are major causes of acetaminophen overdose.*

- *Rivera-Penera noted that it is unclear whether a viral insult alone or ingestion of therapeutic doses of acetaminophen in the setting of a viral insult together lowers the threshold for hepatic injury.*

OSE Review of AERS data on APAP overdose and associated hepatotoxicity (2002)
In 2002, OSE Safety Evaluator Team Leader Claudia Karwoski identified 307 US cases of liver injury associated with ingestion of one or more APAP-containing products reported to AERS between 1998 and July 2001. Twenty-five cases involved children younger than 12 years of age. None of these cases appeared to involve intentional suicide, but the reporter raised questions about child abuse in two cases. The children ranged in age from less than one day old to 8.5 years. Seventeen (60%) were male, seven were female, and gender for one child was not specified. Twenty-one children were hospitalized; fifteen (60%) had severe life threatening liver injury with liver failure; and ten died.

Twenty-two (88%) cases involved use of only one APAP product. Eleven case reports did not specify the category of APAP product used, but of those that were specified, seventeen cases involved use of a single ingredient APAP product. Use of Infant's Tylenol Drops (100mg/ml) and use of Children's Tylenol Suspension (32 mg/ mL) were reported in seven and five cases respectively. Eleven case reports listed an unspecified APAP or Tylenol product. Potential

contributing factors or confounders were noted in 10 cases (co-suspect medicines or medical conditions).

Eighty-four percent of the pediatric cases involved medication errors. Up to 15 patients received an improper dose due to:

- Use of an improper measuring device
- Misinterpretation of label dosing guidelines or instructions provided by a health care provider (HCP)
- Confusion over differing APAP product concentrations: use of APAP concentrated drops (100 mg/ml) instead of APAP suspension (32 mg/ml).

There were four accidental ingestions of an APAP-containing product and five possible forced ingestions (two cases of possible child abuse and three intrauterine fetal exposures with maternal use of 6-10 g/day APAP). The following list summarizes the circumstances surrounding these 25 cases of APAP hepatotoxicity in children:

- Improper dose (15 cases): Thirteen cases (10 with hepatotoxicity) involved APAP doses higher than the 75 mg/kg/day recommended daily dose

- Wrong formulation (3 cases): In 3 cases, acetaminophen concentrated drops (100 mg/ml) were used instead of acetaminophen suspension (32 mg/ml)

- Accidental ingestion (4 cases): Four cases were classified as accidental ingestion of an acetaminophen-containing product. Three children ingested APAP products while a babysitter was sleeping

- Forced Ingestion (5 cases): Two cases of liver injury were felt to be due to child abuse by the individuals reporting the events. The actual APAP dose could not be determined.

- Medication Error NOS (1 case): An 18-month-old child reportedly following a medication error with an unknown APAP product. The report did not include dose, duration of use, or situational circumstance.

Other Published Data on Acetaminophen-Associated Hepatotoxicity in Children

A PubMed search yielded seven articles published since 2002 that are pertinent to this review, and these sources are summarized below.

Nourjah et al (2006)

As previously described, Nourjah et al published a study presenting national estimates of APAP-associated overdoses obtained by analyzing national database data from 1993 - 2001.[28] The authors used six different surveillance systems that included data from emergency departments (EDs), hospital discharges, mortality data, poison control centers, and spontaneous postmarketing adverse drug event reports reported to the Food and Drug Administration (FDA). Study details and database descriptions are in Appendix B. There were 56,000 emergency room visits and 26,000 hospitalizations for APAP overdose. There were 458 deaths due to APAP

hepatotoxicity, 100 of which were unintentional. Data collected on children younger than 17 years are shown in Table 7.

Table 7: Acetaminophen-associated overdoses in children based on data from national databases (1993 – 2001)

Age	NEISS (ED data)	NHDS (Hosp D/C)	National multiple causes of death file	TESS (poison control)		FDA AERS
				Overall	Fatalities	
< 6 years	17 (±3.29)	2 (±0.49)	< 1 (±0.10)	30 (0.06)	1 (0.07)	NA
6 – 16 years	16 (±3.57)	22 (±1.41)	1 (±0.46)	23* (0.05)	2 (0.15)	4**

*Includes individuals ages 6-19 years
**Reviewed only cases involving individuals 12 years and older

In the NEISS database, about 17% of overdoses occurred in children less than six years of age, and about 16% in children and adolescents ages six to 16 years. Six deaths occurred in children less than 6 years of age.

Squires et al (2006)
Squires et al[29] conducted a prospective, multicenter case study collecting demographic, clinical, laboratory, and short-term outcome data on children from birth to 18 years who presented to one of 24 hospitals in the USA, Canada, or UK from December 1999-December 2004 with acute liver failure (ALF). To participate, subjects met the following inclusion criteria:

- No known evidence of chronic liver disease
- Biochemical evidence of acute liver injury
- Hepatic-based coagulopathy defined as
  - PT ≥ 15 seconds or INR ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy (HE) or
  - PT ≥ 20 seconds or
  - INR ≥ 2.0 regardless of the presence or absence of clinical HE.

A standard adult clinical coma grade scale was used for older children, and an adapted coma grade scale was used for infants and children younger than 4 years. Diagnostic criteria for acute acetaminophen toxicity included a toxic serum acetaminophen level based on the Rumack nomogram[30] (Rumack-Matthew nomogram) or a history of an acute ingestion of 100 mg/kg within a 24-hour period.

Reviewer Comment
- *In a personal communication Dr. Squires stated that he is not certain whether the cases reflect accidental, intentional, or unintentional APAP overdose.*

Between December 1999 and December 2004, the study enrolled 348 children. The median ingested APAP dose was 183 mg/kg (range 19.2 to 734.1). The authors grouped subjects into three etiologic categories: acetaminophen (APAP), indeterminate, and all other causes. Forty-eight (14%) children had acute APAP toxicity (79% female, 67% white), and two of these children were younger than three years old. Compared to subjects in the two non-APAP etiologic groups, children in the APAP group were statistically more likely to be white and/or female.

Among the 48 children with APAP-associated hepatotoxicity, seven were admitted with coma grade 3 or 4, including both children under age three years. These were the only children who had a moderate to severe peak coma grade. Eight children required ventilator support and five required pressor support. Three children underwent hemofiltration, and three had plasmapheresis. Seven children received red blood cell transfusions and twenty received fresh frozen plasma. Of forty-six children who were successfully followed to study day 21, forty-five survived without liver transplantation, one survived with liver transplantation, and one died following liver transplantation.

The non-APAP causes of ALF in the other 300 children included: metabolic disease (10%), autoimmune liver disease (6%), non-acetaminophen drug-related hepatotoxicity (5%), infections (6%), other diagnosed conditions (10%), and 49% indeterminate. Total bilirubin $\geq$ 5 mg/dl, INR $\geq$ 2.55, and hepatic encephalopathy were risk factors predictive of death or transplantation. However, 20% of subjects with non-APAP ALF and no encephalopathy died or required liver transplantation.

Squires et al. concluded that acute acetaminophen toxicity is the most common identifiable cause of ALF in children $\geq$ 3 years old (21%), but the frequency of ALF due to APAP toxicity is even higher in adults (40%). Instances involving prolonged or inappropriate dosing were not easily captured by this study due to limitations in the study's data reporting form.

Reviewer Comment

- *In a personal communication, Dr. Squires clarified what the authors meant by "Instances involving prolonged or inappropriate dosing were not easily captured by this study". Namely, the data intake form did not have questions that would pinpoint the exact amount, frequency of use and duration of use of acetaminophen.*

Muniz et al (2004)[31]

This is a case report of a 58-day-old girl who presented to a small community emergency department with a two-day history of fever, decreased appetite, lethargy, and irritability. Her medical and birth histories were uncomplicated. The day prior to presentation, she was evaluated by a healthcare professional and had a normal complete blood count and chest radiograph. The parents, as instructed, gave the baby 80 mg (16.3 mg/kg/dose; 98 mg/day) APAP every four hours for fever and reported strict compliance with the recommended regimen.

The baby was admitted to the hospital with severe dehydration and was transferred to a tertiary care pediatric facility and was listless and pale on arrival. White blood cell count and liver transaminases were elevated. Initial AST was 1070 IU/L and ALT was 490 IU/L. Coagulation studies revealed: PT = 37.6 seconds, INR = 3.4, PTT = 42 seconds. Serum APAP level was 287 µg/mL.

Reviewer Comment

- *According to the National Library of Medicine's Medline Plus website,[32] a therapeutic APAP level "depends upon usage." As of December 13, 2006, these reviewers were unable to find references citing an accepted normal therapeutic range for serum APAP*

levels. For a point of reference, see Appendix C, which shows the Rumack – Matthew nomogram and its application in a specific instance of acute APAP overdose: at 8 hours post ingestion, the toxic serum APAP level is about 100 ug/ml and at 24 hours, it is about 10 µg/ml .

The baby was admitted to the pediatric intensive care unit, intubated, and hydrated. She was treated with N-acetylcysteine, blood transfusions, fresh frozen plasma, lactulose, and tube feedings. Liver enzymes peaked on Day 3 and then declined. Serology for viral hepatitis, HIV, cytomegalovirus, and Epstein-Barr virus were negative. Blood and urine cultures were negative. She was discharged home on Day 10 and at two week follow-up had no residual clinical or laboratory abnormalities.

Yeuh-Ping Liu et al (2005)

Yueh-Ping Liu et al[33] described a case of fulminant hepatic failure due to chronic APAP intoxication in a 10-month-old, 6-kg female infant. To treat a respiratory infection, the mother gave the infant 750 mg APAP (125 mg/kg per day) for 4 days plus ketoprofen (50 mg/day) and ibuprofen (60 mg/day). Fifteen hours after the last dose of APAP, the serum level is 55 ug/ml, which is above the Rumack – Matthew nomogram toxic level (see comment below). The child recovered after treatment with N-acetylcysteine. The authors note that the child's clinical presentation needed to be distinguished from Reye's syndrome. They recommend that emergency physicians consider APAP toxicity in any child who received APAP and who shows signs of acute hepatic dysfunction, even if the APAP level is low.

Reviewer Comment

- *While the Rumack-Matthew nomogram for assessing acetaminophen toxic levels is used to assess single dose acetaminophen toxicity, an acetaminophen level below the toxic level line would not necessarily rule out potential acetaminophen toxicity during chronic use. However, if the time from the last dose were known, then an acetaminophen level above the nomogram line during chronic use would reflect a toxic level.*

Shaoul et al (2004)

Shaoul et al evaluated whether silent acetaminophen-induced hepatotoxicity occurs in children with fever. The authors noted children are generally less vulnerable to acetaminophen toxicity than adults. However, there have been reports of hepatotoxicity following therapeutic or mildly supra-therapeutic APAP doses in children with fever, dehydration, and vomiting. The authors conducted this pilot study to:

- Correlate APAP levels with aspartate transaminase (AST) levels, fever, vomiting, and/or decreased calorie intake
- Determine parental knowledge regarding the medication dosage and hazards of APAP.

The study included 107 children who presented to an emergency room in Haifa, Israel. Upon presentation, the children had been treated with APAP with a mean accumulated dose of 197 ± 165 mg/kg over 2.8 ± 1.8 days. The mean serum level of APAP was 4.7 ± 4.7 µg/ml; the highest APAP level was 24.7µg/ml. All APAP levels were in the safety range of the Rumack-Matthew nomogram. The authors did not find any correlation between serum APAP levels and

vomiting decreased food intake and serum AST levels. Subjects with fevers above 39 ^{o}C had statistically higher serum APAP levels than other subjects.

Reviewer comment:

- *As previously noted, chronic APAP use may result in toxicity at serum APAP levels lower than those suggested by the Rumack – Matthew nomogram.*

Sixteen parents administered a single APAP dose above 20 mg/kg, and in more than half of cases, the dose was recommended by a physician. These children had significantly higher APAP levels (though nontoxic) than children who received lower doses. Some parents exceeded the recommended total daily dose of APAP for their children, often following a physician's recommendation:

- 46% administered a daily dose above 60 mg/kg
- 25% exceeded a daily dose of 80 mg/kg (dose recommended by physician: 60% of cases)
- 6% exceeded a daily dose of 120 mg/kg (dose recommended by physician: all cases)

Only 24% of parents were aware of the possible toxicity of APAP. The authors concluded that APAP is relatively safe including acute ingestions of more than twice the recommended dose over a brief period of about 2 days.

Reviewer comment:

- *In the United States, the recommended maximum daily dose of APAP in children is 75 mg/kg. As in some other countries (see Table 9 on page 29 of this review), the recommended maximum daily dose of APAP is Israel may be 60 mg/kg.*

Losek (2004) [34]

This study assessed demographic and clinical characteristics of children receiving APAP per emergency room standing orders (single dose 10-15 mg/kg) and identified factors associated with supra-therapeutic doses (≥ 16 mg/kg). Losek reviewed the records of 661 children cared for during a 1-week period (Feb 1998) in an urban pediatric ED with a 36,000 yearly census. Among these 661 cases, nurses administered APAP to 156 children, 41% younger than two years of age. The indication for APAP treatment was fever in 90% and pain in 10%. Nineteen (12%) of the children received a supra-therapeutic oral APAP dose (17 mg/kg). Two administered rectal doses exceeded 20 mg/kg, while no oral dose exceeded 20 mg/kg. Four of the 19 children had additional risk factors (less than two years old and acutely ill) for acetaminophen-associated hepatotoxicity. The authors noted that a commonly used pediatric reference refers to 20 to 40 mg/kg as the rectal dose for APAP, although the recommended and standing dose per rectum is the same as the oral dose. The authors recommended that emergency departments with standing orders for acetaminophen review their acetaminophen dose accuracy, particularly for the rectal route. This recommendation was reinforced by Bilenko et al. (2006) who noted a similar tendency to administer a supra-therapeutic dose by the rectal route in their cross-sectional survey study of 201 children presenting to the Pediatric Emergency Department of Soroka Medical Center, Beer-Sheva, Israel in 2002.[35]

Comment:

- *Neither Losek et al. nor Bilenko et al. studied children who received supratherapeutic APAP doses for associated hepatotoxicity.*

Lagerløv et al (2003)

In this qualitative study, Lagerløv et al[36] studied Norwegian parents' management of common childhood illnesses including their use of paracetamol (APAP). Parents of pre-school aged children from six Norwegian public health centers were asked open-ended questions about their perceptions of illness, its impact on the family, the use of APAP, and their sources of medical information. The interviews were audiotaped and transcribed. They found that parents judged their child's fever as a cause of discomfort and danger. Parents regarded antipyretics like APAP as a medicine counteracting disease. APAP was used as an important tool for parents in managing different upsets during childhood illnesses. Some parents did not want medical information saying it only added to the burden of the situation or made them anxious. Parents were only slightly concerned about the side effects of APAP. The authors speculated that OTC status may be a reason why APAP safety and efficacy are taken for granted.

American Academy of Pediatrics (AAP) Committee on Drugs: Acetaminophen toxicity in children (2001)[37]

This AAP, Committee on Drugs Policy Statement listed nine recommendations to help ensure safety of acetaminophen in the pediatric population. Recommendations included: continued guidance for parents at well-child visits, a list of drugs that increase the possibility of APAP toxicity, guidance for healthcare providers regarding recognition of acetaminophen toxicity, and parameters for use of N-acetylcysteine. In addition, the Committee provided a list of conditions or situations that may increase the risk of APAP toxicity (Table 8 below):

Table 8: Conditions and Situations That May Increase the Risk of Acetaminophen Toxicity[38,39,40,41]
Diabetes mellitus
Obesity
Chronic under-nutrition
Prolonged fasting
Family history of hepatotoxic reaction
Concomitant viral infection

Concomitant Dosing of Multiple APAP-containing Products and Other Risk Factors

Due to the multiplicity of products on the market containing APAP, there is a risk that more than one of these products will be used concurrently to treat different symptoms. For example, a child with an upper respiratory infection may receive one APAP medicine to relieve fever and another to relieve congestion and cough. As previously summarized by Newgreen, the following situations put children at increased risk of APAP toxicity:

- dose ≥90mg/kg/day
- child is sick (versus a minor ache or pain)

- under two years of age
- treatment exceeds one day
- co-administration of other products that contain acetaminophen
- co-administration of various enzyme inducers (such as phenobarbital)
- incorrect product selection
- off-label uses.[42]

Accurate Dosing of Acetaminophen in Children

Pediatric APAP dosing recommendations vary from country to country. Table 9 shows the dosing regimens in four countries:

Table 9. Acetaminophen dosing regimens in four countries

Country	Single Dose (mg/kg)	Maximum Frequency	Maximum Daily Dose (mg/kg/day)	Duration of Use (days)
Australia	15	Q 4 hrs, up to 4 times/day	60	2
Canada	By age group*	Q 4 hrs, up to 5 times/day	-	5
United Kingdom	10	Q 4-6 hrs	60	3
United States	10-15	Q 4 hrs, up to 5 times/day	75	3 (fever); 5 (pain)

*In Canada, doses are quoted from 0 months to 12 years in a range of 40mg to 480mg, respectively, to maximum daily doses of 200mg and 2,400mg, respectively.

Currently, the dosing chart for pediatric APAP formulations in the United States increases in 80 mg increments. Even with weight-based dosing, the recommended dose for weights at the upper and lower limits of each dose range do not fall within the 10 – 15 mg/kg recommended dose. A citizen petition (77N-0994, CP 14, S45) submitted to FDA through the Public Docket pointed out a potential mismatch between dosing by weight and dosing by age that could result in higher weight children receiving a less than therapeutic dose and lower weight children receiving a supra-therapeutic dose. The petitioner recommended a dosing scheme that used 40 mg increments for children less than two years of age.

The 40 mg increment dosing schedule suggested by the petitioner would change the recommended dose for children 11 months of age from 80 mg to 120 mg. The 80 mg single dose provides 7.1 mg/kg to 10.7 mg/kg APAP per dose for children between the 10^{th} and 90^{th} percentiles for weight by age respectively. The recommended 120 mg dose provides 9.4 mg/kg to 14.3 mg/kg per dose for children between the 10^{th} and 90^{th} percentiles for weight by age respectively. The revised dosing schedule did not include any changes for children over 2 years of age.

The petitioner requested that FDA provide:

- Weight-based dosing for children weighing 12 or more pounds, accompanied by a statement advising that the age-based schedule dosing should be used only if weight is not known
- Age-based dosing for children 6 months of age and older
- Professional labeling for healthcare professionals only with weight-based dosing for children less than six months of age and weighing less than 12 pounds.

FDA is currently drafting a proposed rule that will include 20 mg dosing increments for APAP dosing for children six to 23 months of age. The rule does not change the 80 mg APAP dosing increments for children two to eleven years of age. The label will include a statement that informs caregivers to use weight based dosing unless the child's weight is not known.

Acetaminophen Hepatotoxicity and Acetaminophen Access in the United Kingdom, Ireland, France, and Canada – are there lessons to be learned?

There are published data on the effects of APAP access and pack-size restrictions on APAP-associated hepatotoxicity from the United Kingdom (England, Wales, and Scotland), Ireland, France, and Canada. A number of factors should be considered when interpreting this data and how it should inform decisions regarding APAP access and pack-size restrictions in the United States:

- Some countries primarily address intentional overdose and do not identify or discuss unintentional or accidental overdose, which is a significant issue in the United States
- Outcomes may be influenced by variations in people's cultures and attitudes about medicine use as well as differences in medical systems and related legislation
- Some studies evaluate initiation of new restrictions in a population that has had no previous legislative restriction on access to or packaging of APAP. Other studies evaluate the effects of repealing access restrictions in populations that are accustomed to having access restrictions in place.

Table 11 summarizes APAP access and package restrictions in a number of westernized countries.

Table 11: APAP access in westernized countries[43]

Classification	Countries	Comments
Unrestricted purchase	United States Canada	Until 1999, the following Canadian provinces and territories had place-of-sale restrictions that limited the sale of all APAP strengths > 325 mg and all packages of > 24 tablets of any strength to pharmacies only: Ontario, New Brunswick, Manitoba, Yukon, Nunavut, and Northwest Territories. The package size limit in France is 8 grams (16- 500 mg tablets)
Pharmacy-only in unrestricted quantity Small pack sizes from general retailers	Australia New Zealand UK (prior to 1998)	
Pharmacy-only in limited pack sizes Small pack sizes from general retailers	UK (since 1998) Ireland	
Pharmacy-only in unrestricted quantity	Denmark	
Pharmacy-only with limits on pack size	Belgium Finland France Germany Sweden Switzerland	

United Kingdom (UK)

In the UK, APAP-associated hepatotoxicity has been a recognized problem since the 1970's. APAP-associated hepatotoxicity accounted for 73% of all acute liver failures cases reported from Kings College Hospital during the years 1987 – 1993. Most overdoses in the UK are suicide attempts.[44] A study conducted in the 1970's suggested that patients in the UK did not know that APAP overdose was dangerous. A study conducted by Hawton et al, in 1995, demonstrated that 62 of 80 patients admitted to a hospital for APAP overdose thought that the drug could cause death and 34 knew that APAP could cause liver damage. However, only 18 subjects knew that harmful effects of the APAP overdose would not show for more than 24 hours.[45]

In September 1998, the British government enacted new legislation that made OTC APAP available only in limited quantities (sixteen 500 mg tablets or capsules per pack). Blister packages are used in some cases but are not required. The government's goal was to reduce the number of APAP-related deaths by about 10%. . APAP regulations in the UK require the following:

- 8 g limit (sixteen 500 mg tablets or capsules) for packages of APAP sold in general retail outlets (non-pharmacy stores).
- 16 g limit (thirty-two 500 mg tablets or capsules) for packages of APAP sold on pharmacy shelves with consumer access
- Pharmacists allowed to supply up to 50 g (one hundred 500 mg tablets or capsules) APAP without a prescription at the pharmacists' discretion and in justifiable circumstances. Larger quantities available by prescription
- Labels or consumer information leaflets required to include the following statement: *Immediate advice should be sought in the event of an overdose, even if you (your child) feel well, because of the risk of delayed, serious liver damage.*
- Labels required to include the statement: *Do not take with other paracetamol-containing products.*

Blister or strip packing is not required but many manufacturers use this form of packaging.[46]

Reviewer comments:

- *Based on reports of compliance with this legislation in various regions of the United Kingdom, there appears to be little or no enforcement of the statutes or punishment for retail stores or pharmacies that violate them.*

- *The restrictions do not appear to have limited the number of packages that an individual could purchase at one time.*

Similar restrictions were applied to salicylates where appropriate. Since the APAP restrictions went into effect in the UK, multiple surveys and evaluations of mortality and sales data have tried to define how these changes impacted incidence and severity of APAP overdoses and APAP hepatotoxicity in various regions of the Kingdom. As shown in Table 12 below, the studies overall suggest some positive impact on APAP-associated morbidity and mortality.

Overall, data from the UK suggest that APAP package size and access restrictions resulted in decreases in APAP-associated deaths, admissions to liver units, presentations to hospitals for overdose, and number of APAP tablets ingested, at least in the initial two years following legislation. There are regional variations and most of these overdoses are considered intentional. There is no data addressing unintentional overdose. In their 2004 review of the effects of restricting paracetamol in the UK, Morgan and Majeed noted that only three studies distinguished between poisonings due to APAP alone and those due to APAP combination drug products. They noted that two thirds of APAP-related deaths and 10% of hospital presentations in the UK involve APAP combination products, like Co-proxamol (APAP + dextropropoxyphene), which are not sold OTC and that this might dilute the observed effects of the legislation.[47] Morgan and Majeed and other commentators criticized the short follow-up time after legislation in many of studies. One of the legislations intents was to reduce household APAP stocks, which may require longer periods of time than those studied. In Scotland, the APAP-associated mortality rates are twice that in England and Wales, and while study data are more limited, they suggest that the legislation did not significantly reduce APAP poisonings or deaths beyond one year post-legislation.

Reviewer comment:

- *In a personal communication, Dr. William Bernal, hepatologist at King's College, England, stated that there is little doubt that both the numbers of patients developing serious (APAP-associated) hepatotoxicity and those with more trivial (APAP) poisoning have significantly decreased since the introduction of sales restrictions and labeling changes (in the United Kingdom). If given the choice, he would without hesitation, again support APAP restrictions and believes that the majority of the hepatology community in the U.K. would as well.*

Table 12: Summary of Studies Evaluating Effects of APAP Package Size and Distribution Limitations on APAP Overdose and Hepatotoxicity in the United Kingdom

Study	Study Period	Location	Data Sources	Findings
Prince et al (2000)	10/1995 to 09/1998 compared to 09/1998 to 12/1999	Northern England	Reviewed records of patients admitted to a liver unit and patients listed for liver transplantation	▪ Monthly number of referrals to the transplant list fell from 3.5 to 2 ($p<0.02$) ▪ Median number of monthly referrals to the liver unit fell from 2.5 to 1 ($p<0.02$) ▪ 25% of referrals were alcoholic or on anticonvulsants Overdose severity remained unchanged.
Turvill et al (2000)	09/1995 to 08/1999	London	Reviewed all records of patients admitted to the Royal Free Hospital with APAP overdose	▪ 21% reduction in APAP overdose cases ▪ 64% reduction in patients requiring treatment with N-acetylcysteine ▪ Savings of 200 inpatient hospital days No change in proportion of overdoses with benzodiazepines.
Robinson et al (2000)	01/1998 to 06/1998 compared to 01/1999 to 06/1999	Northern Ireland	Reviewed all APAP poisoning admissions to five general hospitals in Belfast (N = 594)	▪ Serum APAP concentration at 4-6 hours post-ingestion decreased from 37 to 27 mg/L ($p = 0.003$) Number of patients admitted with APAP poisoning did not change significantly but trended down (398 to 374).
Thomas and Jowett (2000)	02/1998 to 08/1998 compared to 02/1999 to 08/1999	Wales	Reviewed records of 116 overdose patients admitted 6 months before and 112 overdose patients admitted 6 months after APAP legislation.	▪ Number of APAP overdoses decreased from 52 (45%) to 40 (36%) ▪ Number of overdose patients who took more than 16 tablets: 30 (68%) before and 18 (51%) after the legislation ▪ Number of non-APAP overdoses increased from 64 to 72 (often with drug mixtures including tricyclic antidepressants Number of hospital days unchanged
Sheen et al (2002)	1998, 1999, 2000	UK and Northern Ireland	Intercontinental Medical Statistics Services data	The UK OTC supply of APAP declined from 409 million grams (1998) to 166 million grams (2000). Ibuprofen supply up by 74% (26.4 million grams to 46 million grams)
Hughes et al (2003)	04/1995 to 09/1998 compared to 09/1998 to 01/2003	England	Reviewed admissions to Queen Elizabeth Hospital liver unit and the number of patients admitted to the University Hospitals in Birmingham with APAP overdose	▪ Prior to legislation, the average number of admissions per year for APAP overdose was 360. After legislation, admissions decreased to 250/year (31% reduction). ▪ Admissions to the liver unit declined from 76/year before legislation to 38/year after legislation (50% reduction).
Inglis JH (2004)	1990 to 1991 compared to 2001 to 2002	Scotland	General Registrar Office annual reports: deaths and emergency admission data	▪ After the 1998 legislation, APAP-associated deaths fell 45% in the first year but rose in the 3 subsequent years to reach pre-restriction levels. ▪ With the restrictions, APAP poisonings fell by 14% the first year and stayed lower the second year but increased 10% in each of years three and four to new record highs.

continued

Table 12: Summary of Studies Evaluating Effects of APAP Package Size and Distribution Limitations on APAP Overdose and Hepatotoxicity in the United Kingdom

Study	Study Period	Location	Data Sources	Findings
Hawton et al (2001, 2004)	1993 to 9/1998 compared to 9/1998 to 2003	England Wales Scotland	▪ Data on drug related deaths from the Office for National Statistics (1993 – 2001) ▪ Liver transplants and referrals to all liver units except one in England and Scotland (1996 – 2002) ▪ APAP self-poisoning presentations to five general hospitals (1997 – 2001) ▪ Statistics on sales of analgesics to pharmacies in the UK before and after 1998 legislation	▪ The three years after legislation showed sustained decreases in deaths due to single ingredient APAP (-29%) or salicylate (-46%) products. Similar decreases occurred with combination products. ▪ On the basis of mortality data from 1993 to 1998, 118 deaths involving APAP and 81 deaths involving salicylates were avoided. ▪ Deaths involving ibuprofen were few: 11 deaths in the five years before legislation and 13 deaths in three years after legislation. These deaths also involved other drugs. ▪ There was a 30% reduction in admissions to liver units for APAP induced hepatotoxicity. Mean annual admissions for APAP poisoning decreased from 349/yr from 1996 – 1998 to 230/yr from 1998 to 2002. ▪ During the first year after legislation, hospital presentations for APAP overdose decreased by 9 – 21% but no further decreases occurred thereafter. The number of ibuprofen overdoses increased by 11 – 44% in the second and third years after legislation. ▪ The number of tablets ingested in APAP and salicylate overdoses decreased significantly during the 3 years after legislation. ▪ The total numbers of APAP tablets sold was similar before and after legislation. Pack size went down and number of packs sold went up.
Bateman et al (2006)	1995 to 1998 (Q1) compared to 1998 (Q2) to 2000 (Q2) compared to 2000(Q3) to 2004	Scotland	▪ General Register Office for Scotland: for overall deaths by APAP poisoning with and without alcohol or co-ingested medicines, overall, APAP + propoxyphene, and APAP + codeine ▪ APAP overdoses from acute hospital discharge database ▪ Prescription data for APAP compounds	▪ Focused on in-hospital deaths which they felt more likely due to APAP effect. Most out-of-hospital deaths involved other drugs whereas the majority of in-hospital deaths involved APAP use with or without alcohol. Overall most deaths involved co-proxamol (APAP + propoxyphene). ▪ The number of APAP-related overdoses decreased among children under age 10 years and among youths ages 10 to 19 years. However, overdoses increased among adults and the elderly. ▪ The authors noted that poisonings overall were increasing in Scotland in the 1990's and then declined. This makes it more difficult to interpret legislation effects; however, it appears that the legislation has been unsuccessful in Scotland.

Other countries
In France, APAP is a commonly used analgesic but the content of each pack of APAP has been legally limited to 8 grams since the 1980's. Liver failure due to APAP has always been much less common in France than in the UK. France has fewer than 10 cases of APAP-induced liver failure per year (as of the year 2000).[48]

In 1997, the Republic of Ireland introduced tighter APAP packaging restrictions than the UK. These restrictions were recommendations until 2001 when they became law. Emergency supplies of 12 tablets are available for general retail sale, and packets of 24 tablets can be purchased at the pharmacy. These limits parallel restrictions in Finland that were introduced in 1976. In 2000, Donohoe and Tracey examined 2020 cases (1044 in 1997 and 976 in 1998) of acute intentional APAP poisoning. More than 50% of cases involve ingestion of 24 or fewer tablets with no significant difference between the two study years. There was a statistically non-significant decrease in the number of poisonings with 48 or more ingested tablets. The authors concluded that the voluntary reduction in pack size did not result in a decrease in APAP overdose. However, the study did not evaluate any change following legislation reducing pack size. It is important to note that APAP was blister packaged in Ireland even before the 1997 recommendations and the 2001 legislation that reduced pack size.

Data from Canada suggest that provinces with long standing restrictions on package size have lower annual rates of hospitalization for APAP overdose than provinces where APAP distribution was unrestricted for more than 30 years. In 1999, remaining provincial restrictions on the sale of APAP were lifted. Comparing the 1.5 year periods preceding and following the statutory change, there were no changes in the annual incidence rates for acetaminophen overdose hospitalizations. The study was conducted by McNeil Consumer and Specialty Pharmaceuticals, and the authors did not comment on the lower rates of hospitalizations for APAP overdose in provinces and territories with package size restrictions. **It is possible that individuals who grow up with APAP in small packages and with restricted access develop different beliefs and attitudes about APAP that lead to different use behaviors.**

Comment:

- *The introduction of new APAP access and package restrictions to a population of consumers, who have had unrestricted access, is different from removing APAP restrictions in an area where consumers have been accustomed to restrictions for many years. Legislation changes that alter consumer access to APAP will probably lead to different effects on consumer APAP use behaviors based on consumers' baseline attitudes and beliefs about the safety and efficacy of APAP as a medicine and as a mechanism for suicide. Individuals who have grown up with restricted access to APAP may view the drug differently than individuals who have grown up without such restrictions.*

When extrapolating these data from the United Kingdom and other countries to the United States population, a number of differences should be considered. Cases of acetaminophen overdose in the United Kingdom are nearly exclusively associated with intentional overdose. In the United States, it appears that about 10-15% of acetaminophen overdoses and about 25-30% of acetaminophen-associated hepatotoxicity cases involve unintentional overdose. This difference

may, in part, be due to a different threshold for nonessential use of medicines. The positive impacts of blister packaging and package size restrictions may differ in size and character for American consumers with intentional APAP overdose and American consumers with unintentional APAP overdose. For example:

- If an individual uses an APAP product and does not achieve adequate pain or fever relief, the individual may take more drug, take a different drug, or contact a healthcare professional for advice. With blister packaging that includes prominent warnings and directions for use, a person is more likely to recognize how much drug they have consumed over a given period of time (e.g. over a day) and the repercussions of overdose. Perhaps this will increase the likelihood of seeking advice from a healthcare professional before unintentional APAP overdose occurs.

- An individual who impulsively chooses to make a suicidal gesture with APAP overdose may have time to reconsider their actions if they have to pop each individual tablet or capsule out of a blister pack and read a liver toxicity warning while doing it.

- Regardless of package size limitations and package configuration, an individual who is truly suicidal and plans out a suicide by APAP overdose may take all actions necessary to have a fatal dose of APAP available. However, data from the United Kingdom suggests that the size of the overdose may decrease when package sizes are smaller and blister packaging is used. In addition, empty blister packages sometimes allow family to accurately report the amount of drug consumed to hospital personnel caring for an individual with APAP overdose in the emergency room.

Minimizing Acetaminophen-Associated Hepatotoxicity: Exploring Intervention Options

The next portion of this paper presents potential regulatory actions followed by potential educational outreach approaches for both healthcare professionals and consumers. This list, while comprehensive, may not include all possible ways to effect change.

1. Limit OTC package size

Data from the U.K. suggests that package size restriction may reduce the occurrence of intentional and unintentional APAP overdose. These restrictions were put in place primarily to reduce the occurrence of intentional overdose. In the United States, unlike in the U.K., intentional APAP overdose is not one of the primary methods for committing suicide. So, it is not clear whether package restrictions in the United States would have the same impact as in the U.K. or whether the effect on APAP hepatotoxicity would be more or less robust.

OTC acetaminophen package sizes could be limited to 36-count packages for 325 mg solid dosage forms and 24-count packages for all 500 mg solid dosage forms, as was done in the U. K. This package size would provide enough acetaminophen for maximum dosing for three days for an adult. This is the current labeled duration of treatment for fever. The current duration of treatment for pain in adults is ten days. However, after three days of pain treatment, a consumer

would need to decide whether to start a new package of APAP or to speak with a healthcare professional.

Pros:

- Evidence from the U.K. experience suggests that limiting package size may reduce the number of pills ingested on impulse due either to frustration with unrelieved pain or suicide gesture/intent.
- In addition, despite some noncompliance in the general sales stores and pharmacies with package number sales restrictions, there has still been a reduction in overdoses.
- More obvious when a lot of drug is being used over time – may make a consumer more likely to recognize that adequate pain relief is not being achieved with correct use and that a healthcare professional should be consulted
- If an individual needs APAP to treat their fever or pain for more than three days, they need to actively decide whether to start a new pack of medicine. It is possible that this active process of finishing one pack of medicine and starting another may lead some consumers to consider whether to consult a healthcare professional before continuing self-treatment.
- The monograph already has package size restrictions on some products (e.g. sodium phosphate, flavored aspirin for children, fluoride toothpaste).

Cons:

- In the past the Office of Chief Counsel has raised questions about whether we have the legal authority to limit package size (e.g. ephedrine). Industry may argue that we do not have the authority.
- It is not clear that data from the U.K. predict what would occur in the United States. The U.K. restrictions were intended to reduce intentional overdoses. It is not clear how package size restrictions would impact *unintentional* APAP overdoses.
- Family members will need to purchase packages of acetaminophen more often (but probably not more often than they need to go to the grocery store or pharmacy for other items).
- The products will likely cost more to purchase in smaller packages.
- Many people who use acetaminophen correctly may be upset by package size restrictions and increased product cost.
- Individuals, who use APAP regularly to control the symptoms of osteoarthritis and degenerative joint disease, would need a cost effective mechanism to purchase larger quantities.
- It is not clear whether package size restrictions alone would limit the number of APAP packages that an individual could purchase at one time. The value of restricting the *number* of packages at purchase would need consideration.
- If the United States decided to restrict APAP package size and the number of packages that could be sold at point of sale, then legislation would need to include consequences for noncompliance and consideration of enforcement measures.
- Pharmaceutical companies and retailers will not readily agree with this.

2. Require blister packaging for OTC with enhanced labeled warnings on the blister packs.

Research on consumer warnings suggests that a product warning is more effective when users must physically interact with it during product use. [49] This means that the warning is placed where it temporarily interferes with task accomplishment and thus increases the likelihood that the warning will be processed in a meaningful way. Such warning placement interrupts a person's *script* or routine and demands attention. In a comparative study, versions of warnings placed where they interrupted the users interaction with the product produced 46% compliance compared to 10% compliance for warning placements that did not interfere with task accomplishment. Studies with medications and non-medication products show that placement of the warning on the product itself (rather than the outer carton) increases the likelihood of a user noticing the warning.[53]

Packaging acetaminophen-containing products in cardboard wrapped blister packs could offer this physical interaction at the time of drug use. Key safety messages and directions for use could be repeated in larger font size on the cardboard face adjacent to the blisters, forcing the consumer to see this information each time the product is used. For example, this packaging method could work with a multi-day treatment card where the card contains 8 to 12 grams APAP (16 to 24 tablets of APAP 500 mg) or with daily blister pack cards that come in a box containing 7 or 14 daily cards.

Changes in package configuration should be considered for OTC APAP-containing drugs. For solid dosage forms, tablets and capsules should be packaged in labeled blister packs that contain additional visual reinforcements of warnings and directions for use. Pop-out blister packs encased in a card would allow portability of the product with all of its drug information. It would also provide a mechanism for keeping track of how much drug was taken that day. The number of missing units from a blister pack is a visual signal to a consumer whereas, it is not possible to tell whether there are two fewer tablets in a bottle of 100 tablets.

Pros:

- Consumer can see how many pills have been used. A blister pack or card provides a visual reminder of how many tablets or capsules have already been used. This may reduce unintentional double dosing.
- Makes impulsive chugging of more than two pills less convenient
- Allows additional surface area on packaging to reinforce key warnings and correct dosing information if the blister pack is enveloped in a cardboard casing.
- There are some published data on the use of blister packs or blister calendar packs to improve compliance with single or multi-drug regimens for prevention of graft rejection and treatment of malaria, tuberculosis, leprosy and sexually transmitted infections.[50,51,52]

Cons:

- Harder for older individuals with arthritis to get the pills out, but these individuals could obtain prescriptions for the drug.
- Packaging may be more expensive which could translate into greater drug cost to the consumer.

- Does not address use with liquid formulations.
- This is likely to raise legal issue(s) with the Office of Chief Counsel.

3. Consider removal of acetaminophen from some or all OTC combination drugs

Surveys conducted among consumers and information gathered from patients with acetaminophen-associated hepatotoxicity suggest that many consumers are not aware that acetaminophen is in some of the OTC and prescription products that they use. This results in unintentional overdose when more than one drug product is used concurrently. A similar and more common problem occurs with concurrent use of a prescription pain reliever and an OTC pain reliever or combination drug product with acetaminophen. Labels for prescription drugs are regulated by State Boards of Pharmacy. They are not standardized and do not always clearly inform patients/consumers about the drug's active ingredients.

Reviewer comment:

- *This regulatory change could be considered for ibuprofen and naproxen products as well as acetaminophen products to encourage consistent medicine decision-making across the class of pain reliever/fever reducer products. The purpose of this regulatory change is to minimize the unnecessary and unrecognized use of all OTC analgesic/fever reducer active ingredients.*

Pros:

- May decrease the likelihood of a consumer using two OTC APAP-containing products concomitantly, such as a combination product to treat congestion and cough and another product for headache

Cons:

- Convenience factor of combinations is eliminated.
- Forces consumers to buy their fever reducer/pain reliever separately and take two medicines rather than one when they have a combination of symptoms that happen to include fever or headache.
- Industry is likely to actively resist this because it will eliminate many products from the market.
- It is not clear what data we could use to support this other than it makes sense that fewer products would likely lead to fewer episodes of concomitant use of more than one OTC APAP-containing product.
- This is likely to raise legal issue(s) with the Office of Chief Counsel.

4. Modify and expand label warnings included in the Proposed Rule for internal analgesics warnings

Currently, OTC acetaminophen-containing products are not required to carry an organ specific warning except for that associated with the alcohol warning:

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

In December 2006, FDA published a Proposed Rule that included (among other warnings) the following liver warnings for adult acetaminophen products and pediatric acetaminophen products (71 FR 77314 @ pg 77349-50):

Adult formulations:

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

- *more than (max # daily dosage units) in 24 hours*
- *with other drugs containing acetaminophen*
- *3 or more alcoholic drinks every day while using this product*

Pediatric formulations:

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

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

The warnings in the Proposed Rule provide the needed liver specific warning for acetaminophen-containing products. It makes sense to combine the alcohol warning with the liver warning since chronic alcohol use is one factor that may contribute to APAP-related hepatotoxicity. However, small changes in the wording of the warnings and incorporation of information related to gender differences may help to optimize accuracy, comprehension, and impact. Women develop adverse health consequences from the use and abuse of alcohol over shorter time periods and with lower consumption than men.[53] On average, women are smaller and tend to have a higher percentage of body fat and a lower percentage of body water than men. Therefore, if a man and a woman of the same weight ingest the same amount of alcohol, the woman will tend to achieve a higher blood alcohol concentration.[54] As a result, we may need to consider incorporating weight and gender-related differences for alcohol consumption into the liver warning language on adult APAP formulations.

In addition, published data and additional data presented at the NIH Acute Liver Failure Workshop (December 4, 2006) suggest value in requiring the following two warnings on the *Drug Facts* label for all APAP-containing drug products:

Ask a doctor before use if you

- use prescription pain medicines
- have hepatitis or other liver disease. You may need a different dose.

Reviewer comment

The Proposed Rule has the following wording: "Do not use with any other drug containing acetaminophen (prescription or nonprescription). Ask a doctor or pharmacist before using with other drugs if you are not sure" and "Ask a doctor before use if you have liver disease."

While not all people heed label warnings, there are some data suggesting that label warnings will be read by consumers. A 2004 study by Nabors et al assessed label reading in 876 high school and college students. Most reported reading labels or package inserts to learn about medicines. Participants experiencing pain (except headaches) were more likely to read the labels. Participants were interested in information about side effects, ingredients, dosage instructions, and symptoms related to use.[55]

Pros:

- Research on consumer warnings suggests that providing more explicit or detailed information in a warning message increases the warning's effectiveness.[56]
- The more explicit warnings may encourage patients/consumers to initiate a dialogue with their healthcare professional about concomitant use of multiple drug products for treatment of pain, thereby avoiding unintentional acute or chronic APAP overdose.
- Data presented by Julie Polson, M.D. at the NIH Acute Liver Failure workshop suggest that individuals with hepatitis may have a lower threshold for APAP-associated hepatotoxicity with use of recommended doses of APAP.[19]

Cons:

- More information to read on the label, which could theoretically detract from comprehension of other label elements.
- Some people don't read the labels now, so it is not clear that they will read new warnings.

5. Acetaminophen identification: principal display panel (PDP) requirements

The Proposed Rule for acetaminophen warnings includes a requirement that the name *acetaminophen* appear on the principal display panel, as part of the established name, for all OTC drug products containing acetaminophen. The Proposed Rule includes the following requirements for size and appearance of the word *acetaminophen* on the PDP:

> *Manufacturers determine the prominence of the name "acetaminophen" on the PDP by selecting from the two options listed below, the print size option that is greater:*
> - *the name "acetaminophen" is at least one-quarter as large as the size of the most prominent printed matter on the PDP or*
> - *the name "acetaminophen" is at least as large as the size of the "Drug Facts" title, as required in 21 CFR 201.66 (d)(2).*
>
> *The name will be highlighted (e.g. in fluorescent or color contrast) or in bold type so that the name is prominent and stands out from other text.*

In addition, FDA should consider standardizing the appearance of these words on the PDP in terms of font and color contrast to maximize rapid consumer recognition. Because packages are many different colors, it may be necessary to come up with a design that ensures prominent appearance on all color backgrounds. Consumer warning research suggests that color is one of

the most important features that can help a warning stand out, and the effectiveness of the color depends on sufficient contrast from its surroundings. The three color combinations that provide the greatest contrasts are: black on white; black on saturated yellow; and white on saturated red. Other data support the use of mixed case type in a simple font without serifs (like Arial) except where the print is very small. This information should be used to define a limited number of options for the color and appearance of the active ingredient name on the PDP's for acetaminophen, NSAID, and aspirin containing products.[57]

Pros:

- Establish rapid consumer recognition of APAP as an active ingredient in APAP-containing products.
- More obvious to consumer when two drug products both contain APAP. This may decrease incidences of unintentional overdose through concomitant use of two APAP - containing products.

Cons:

- For this change to have impact the consumer needs to understand that taking too much APAP can be harmful. Also, the consumer needs to read and adhere to the label warning that states: *Do Not Use with other products containing acetaminophen*.

6. Restrict the number of different dosage strengths by standardizing acetaminophen concentration for all liquid dosage forms and for pediatric solid dosage forms.

Currently, there are two concentrations for liquid/suspension formulations of acetaminophen: 80 mg/5 mL (suspension) and 80 mg/0.8 mL (concentrated drops). Published studies suggest that parents confuse dosing across these two different pediatric product concentrations and that many parents mistakenly believe that the infant drops (80 mg/0.8 mL) are less concentrated than the children's suspension.[58,59] Some investigators have argued that all non-solid acetaminophen dosage forms for adults and children should contain 80 mg/0.8 mL and that these dosage forms should include a measuring syringe marked with all of the weight-based doses included on the label.[60,61] Products labeled for adults could provide a syringe or a cup that successfully delivers the correct dose.[62] While data suggest that the acetaminophen concentrated infant drops are associated with more dosing errors than the children's suspension, it is not clear that this would be the case if the suspension concentration was not available. The use of the higher concentration would allow easier dosing in small (and possibly all) children and would allow the use of the same drug concentration and dosing calculations for all consumers from infancy to adulthood.

Sponsors could be restricted to marketing the fewest number of pediatric solid doses needed to accommodate the labeled dosing range from ages 2 to 11 years. Marketing of more than one pediatric solid dose formulation, where one formulation might conveniently cover the full pediatric dosing range, may cause consumer confusion. This is especially true if the packages and pills look very similar. For example, McNeil Consumer Health manufactures two dosages of Tylenol Meltaways – an 80 mg tablet and a 160 mg tablet. Both tablets are pink or purple and chewable. Both packages look nearly identical except that one is called *Jr. Tylenol Meltaways*

(160 mg) and one is called *Children's Tylenol Meltaways (80 mg)*. The *Jr. Tylenol Meltaways* is labeled for children ages 6 years and older. The *Children's Tylenol Meltaways* label includes dosing for children ages 2 to 11 years of age with the lowest recommended dose being 2 tablets. Confusion may occur when dosing children, especially if both products are available in the home and more than one child is being dosed.

If a situation arises where two different tablet strengths are needed to accommodate convenient and correct dosing for all ages, then the packaging of the product should clearly distinguish the two strengths using differences in name, color, and explicit communication about tablet strength and ages for use.

Reviewer Comment:

- *This process can be easily monitored and overseen with NDA products. Defining this process for Monograph products would be challenging but worthwhile in order to ensure ongoing availability of chewable dosage forms for children.*

- *This concept could be applied to ibuprofen and naproxen products as well.*

Pros:

- One dosing scheme and one drug concentration for acetaminophen liquid dosage forms may reduce medication errors/overdose caused by use of multiple products with different dosing schemes. This may benefit use in children and in adults.
- Minimizing the number of pediatric solid formulation strengths may decrease medication errors especially if different strengths are visually demarcated by differences in color, and perhaps size, with clear labeling that emphasizes differences.

Cons:

- If the infant concentrated drops are available, but not the suspension (liquid), then the product with the most dosing errors is retained (see discussion below). If the children's suspension (liquid) is available, but not the concentrated drops, then it may be difficult to get infants to swallow an adequate dose.
- If the suspension is removed from the market and healthcare professionals are not well informed of this change, an increase in pediatric APAP overdose and APAP-associated hepatotoxicity could occur. Physicians could erroneously instruct parents to treat their children based on the dosing recommendations for the less concentrated suspension.
- It is not clear whether there is sufficient data to support this restriction. Most known cases of APAP toxicity following an overdose with an inappropriate or incorrect dosage strength are case reports.

7. Change dosing so that single maximum dose is up to 650 mg and/or maximum daily acetaminophen dose is less than 4000 mg per day.

Revision of the single dose and/or maximum daily OTC acetaminophen dose could be approached in one of two ways:

Remove the 500 mg unit dose from the OTC market (could be available Rx). Leave the 325 mg unit dosing the same

Pros:

- Makes the 500 mg tablet less accessible, and encourages consumers to use the lowest effective acetaminophen dose for the treatment of pain and fever.
- People who may be more sensitive to the toxic effects of APAP (it is not clear who they all are) will use a lower dose if they follow label instructions.

Cons:

- Efficacy and safety data suggest that 1000 mg of acetaminophen offers greater efficacy than 650 mg acetaminophen for the short-term treatment of acute pain (two studies on post-delivery episiotomy pain) with a similar safety profile.[74]
- Dose ranging data for fever reduction may not be available.
- Lower efficacy with the 650 mg dose could lead to more frequent dosing without lowering total daily dose or could lead to concurrent use with other OTC pain reliever/fever reducer drugs.
- If consumers fail to achieve adequate pain relief, they may take more medicine than instructed on the label despite any label warnings about the risks of hepatotoxicity.
- Industry is unlikely to support this change.
- Most people are not at risk for liver toxicity with the 4000 mg /day total dose.

Leave 500 mg and 325 mg units in the monograph but change the total daily dose to 3.0 to 3.25 g: For 500 mg Extra-Strength formulations: take 1-2 tablets every 6 hours up to 3 doses per day. For 325 mg Regular Strength formulations: take 2 tablets every 4 hours up to 5 doses per day.

Reducing the total daily dose of acetaminophen to 3.25 g/day may be the more reasonable of the two options; however, both options may add to, rather than reduce, the unintentional overdose problem. Acetaminophen is effective at relieving mild to moderate pain for some people. The 1000 mg dose is more effective. Failure to obtain pain relief with lower doses may encourage greater deviation from recommended dosing due to poorer pain control. Strong label warnings, package size limits, and package configuration changes combined with strong, clear educational messages may be more likely to change consumer behaviors in ways that improve drug use safety than regulatory measures that decrease the efficacy of the drug.

Pros:

- The 500 mg dose of APAP remains available. This is the most commonly sold dose unit of APAP. There are data that support that a 1000 mg dose of APAP is more effective than 650 mg APAP for relief of pain.
- The lower maximum daily dose is less likely to cause hepatotoxicity in more susceptible individuals.

Cons:

- Changing the directions for use on the label of the 500 mg dose unit bottles may not change overuse behaviors driven by persistent pain. The label directions are already being ignored.
- The duration of effect for acetaminophen may leave some consumers with a six hour period of time where they do not have adequate pain or fever control.
- It is rare for an individual to develop acetaminophen-associated hepatotoxicity using 4 grams per day of acetaminophen. While this may occur more often in chronic users and abusers of alcohol and individuals with anorexia with or without viral illness, label warnings could address these groups. Other populations with increased risk can not be readily identified at this time.

8. Package Insert for all OTC acetaminophen-containing medicines

A package insert (PI) could reinforce warnings on the Drug Facts label. The PI could caution consumers against concomitant use of different APAP-containing products to treat different symptoms. The insert could also inform consumers that some prescription pain products contain APAP and should not be used concomitantly with OTC APAP-containing products.

Pros:

- Reiterates information on warnings and correct use of APAP-containing products to consumers.

Cons:

- Consumers may not read the PI. This may not be an effective means through which to communicate risk. Unless the materials are read and lead to retained information, any benefit will remain unrealized.

9. Educational initiatives for healthcare professionals

- **FDA science paper with complementary healthcare provider information sheet and patient information sheet through the Drug Safety Board**
  This information could be announced with a press release. The professional trade press often picks up this information and draws attention to it.

- **Articles and/or letters to the editor in professional journals about issues with unintentional overuse of acetaminophen-containing products and hepatotoxicity**
  This initiative should begin when regulatory changes become public. Articles from FDA should summarize the acetaminophen toxicity issue in the United States and then focus on the regulatory and educational actions being taken and methods for follow-up of effects of these changes over time.

- **CME module on Safe Pain Management**
  Teach providers to inform their patients about the active ingredients in their prescription pain relievers and how they correspond with OTC analgesics. Healthcare providers need to provide explicit information to patients about prescription medicines that can and can not be

used with various OTC analgesics. Encourage professional associations and other organizations that offer online CME to offer the module on their websites.

- **Dear Healthcare Professional Letter**
  Present and explain package and labeling changes for OTC drug products containing APAP.

Pros:

- These initiatives could broaden awareness of combination products containing APAP.
- These initiatives could heighten awareness of unintentional overdosing through concomitant use of multiple acetaminophen-containing products.
- These initiatives could encourage prescribers to inform their patients when their prescription analgesic contains acetaminophen and to warn them against using their analgesic with OTC products containing acetaminophen.

Cons:

- Considerable Agency time and monetary resources may be needed to prepare and disseminate educational materials for these initiatives.

10. Educational initiatives for consumers

The consumer educational campaign should occur in two phases. Phase I would precede any proposed regulatory changes and could enter planning and development immediately. Phase II would begin with publication of any and all regulatory changes and continue. In addition, FDA could partner with other government agencies, such as the CDC, to advise and educate consumers about drug-induced liver toxicity. While some consumer education about APAP has been done it is clear that more is needed.

Phase I: Pre-Regulatory

OTC Medicines are Serious Medicines: Getting to Know Your Medicines for Pain and Fever

- **Goals:**
  - Change consumer belief that OTC medicines are innocuous. Teach that OTC medicines are serious medicines and can be harmful if used incorrectly.
  - Build consumer awareness of safe use of OTC medicines, especially analgesics. Teach use of the Drug Facts label and simple do's and don't about using medicines.
  - Introduce consumers to the organ specific risks associated with analgesic use and overuse. Focus on knowing active ingredients in both OTC and prescription medicines.

- **Educational Messages**
  Would include the following:
  - Read the label. Know your active ingredients and what they do.
  - Do not take two medicines that contain the same active ingredient at the same time (not in the same dosing window)
  - Do not take more than recommended. If the medicine does not work, do not take more. Call your doctor or pharmacist.

- Do not take for longer than directed. You may have a more serious problem. Call your healthcare provider.
- Measure your liquid medicine with a medicine measuring tool
- Keep track of when you use your medicine and how much you use
- More is not better. If the recommended dose of medicine does not work for you, it may not be the right medicine for your problem. Call your doctor or pharmacist for advice.
- Tell your healthcare providers about ALL the medicines you use….the over-the-counter ones too.
- Discuss how some people may be more at risk for liver toxicity due to underlying liver disease or alcohol intake.

- **Routes of Dissemination**
  Could include the following:
  - Press Release
  - PSA's (consider resurrecting the black PSA from the 2004 campaign with modifications based on focus group feedback)
  - Medicines in My Home website lesson on "Pain and Fever Medicines" (target audiences: adult, parents, secondary school teachers and students)
  - FDA and You article on "Pain and Fever Medicines" (target audience: secondary school teachers and students)
  - Partner with NIH to create educational materials: web and print

Phase II: With and Post-Regulatory Changes
A "Have You Noticed?" Campaign

- **Goals:**
  - Encourage consumers to link changes in the appearance, size, and configuration of their analgesic-containing OTC medicines to the importance of using these medicines correctly and the dangers and risks of overuse.

- **Educational Messages**
  The following messages should be the focus of Phase II of the educational campaign and should also reinforce the messages from Phase I of the educational campaign:
  - You may have noticed that medicines for pain and fever look different than they used to. These changes will help you: know the active ingredient in your medicine, choose the right medicine for your problem, and use the right dose at the right time.
  - It is important to choose and use a medicine with an ingredient for pain or fever only if you have pain or fever.
  - You should not use two medicines that contain the same active ingredient at the same time. All medicines that contain a pain and fever ingredient now have the name of the ingredient on the front of the package where you can see it right away. Look for the word *acetaminophen, NSAID, or aspirin* on the front of your medicine package.
- **Routes of Dissemination**
  - Press Release
  - Drug Safety Board patient information sheet
  - Message from the Surgeon General
  - Major news network health coverage and news magazine coverage

- Report on National Public Radio
- Through formal partnerships with organizations and associations that promote consumer health and education.

Pros:

- Educational campaigns have been successful in the past in changing risky behaviors and decreasing the occurrence of adverse events.
- Much can be accomplished if resources are adequate.

Cons:

- There is limited funding available.
- A campaign addressing APAP overdose and toxicity was initiated in January 2004 and the problem continues.
- An educational campaign may receive complaints from industry if limited to acetaminophen rather than safe use and the risks of misuse of all OTC analgesic active ingredients.
- An educational campaign without regulatory change may have limited impact. Advertising for APAP products, unlimited package sizes, and the multitude of products available on store shelves may undermine education.

11. Research to identify susceptible populations and safe dosing in these populations

The literature suggests that certain populations may be at increased risk for acetaminophen toxicity. Examples might include those who abuse alcohol or who consume more than 3 alcohol drinks daily, patients with fever, malnourished individuals, and patients with liver disease. However, the data is not definitive even with alcohol overuse or abuse, as some researchers assert a lower risk in chronic alcoholic individuals versus individuals who have just recently stopped drinking alcohol.[70] Additional research in identifying populations at increased risk and the safe dosing in these groups is needed.

Pros:

- Research can help identify what populations or clinical situations need a modified dose or avoidance of acetaminophen.
- May help to avoid limiting use of acetaminophen in populations not at risk.

Cons:

- Research is expensive and time-consuming. It may be years before data is available and acetaminophen overdoses will continue unabated.

Summation

The interaction of the educational programs with regulatory changes is very important. Consumer warning research has shown that the more hazardous a consumer perceives a product to be, the more likely the user will look for and read warning information. Product-users are less likely to read warnings on more familiar products or to even look for or notice warning information on such products. Experience and frequency of product use contribute to a person's familiarity with a product, but people may also consider themselves familiar with a product based on: seeing it used, interacting with advertising, or experiencing other products perceived

as similar.[63] One year after full implementation of the regulations governing the OTC Drug Facts label, the NCPIE conducted a survey of 1009 adults and found that 40% of adults consulted the label for active ingredients and 20% looked for information on side effects and other warnings. Consumer warning experts suggest that this low percentage of warning attendance may reflect a widespread consumer belief that any drug sold OTC must be safe and free of any serious side effects. This paper suggests a combined regulatory and educational approach to address the morbidity and mortality associated with unintentional and intentional acetaminophen overdose in the United States. Required changes in the package label information, package size, and package configuration may reduce consumers' familiarity with acetaminophen and encourage consumers to:

- link physical package changes to educational messages and more prominent, redundant warnings
- link warning messages to a desire to comply with labeled directions for use.

Through a multi-faceted intervention, FDA hopes to maintain the benefits of nonprescription acetaminophen availability while minimizing acetaminophen-associated hepatotoxicity in adults and children.

PubMed Search Terms Used

Acetaminophen and pediatric overdose
Acetaminophen toxicity in children
Acetaminophen and pediatric heptatoxicity
Acetaminophen and paracetamol and liver failure
Acetaminophen and paracetamol and hepatotoxicity
Acetaminophen and paracetamol and overdose
Blister packs and compliance
Acetaminophen dosing and children

Appendix A:
APAP Mechanisms of Toxicity, Concomitant Risk Factors, and Inter-Individual Differences

Mechanisms of Toxicity

Acetaminophen itself is not toxic. Cellular injury is caused by its unstable metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is normally present in small amounts and is rapidly neutralized by conjugation with glutathione. Toxic levels of NAPQI accumulate when large amounts of substrate are available for metabolism or the metabolism is accelerated by enzyme induction, as in individuals who regularly consumer alcohol or use medications that cause enzyme induction, like anticonvulsants. In these situations, the hepatic pool of glutathione is depleted, permitting accumulation of NAPQI and subsequent hepatotoxicity. Studies suggest that fasting and malnutrition may also be risk factors that lower the threshold for hepatotoxicity.

At therapeutic doses, acetaminophen is predominantly metabolized by glucuronidation (52-57%) and sulfation (30-44%) conjugation reactions with less than 5% of the drug metabolized by oxidation to NAPQI.[64] In clinical situations involving acute or chronic overuse of acetaminophen (whether unintentional or intentional) or concomitant predisposing factors, the glucuonidation process can become overwhelmed, forcing increased acetaminophen metabolism through the oxidative pathway. When this occurs, the reactive acetaminophen metabolite binds to important hepatic intracellular proteins, resulting in cell death. This process creates acetaminophen-protein adducts that are detectable in serum and may serve as a biomarker of acetaminophen toxicity.[65]

The APAP-induced hepatocellular injury results in a prolonged rise in liver-derived transaminase and alkaline phosphatase serum levels.[1] Without timely intervention, fulminant hepatic failure can ensue.[66] When given early in the hepatotoxic process, oral and intravenous N-acetylcysteine are effective in minimizing acetaminophen-induced liver injury. Methionine is approved for treatment of acetaminophen overdose in other countries.

Concomitant Predisposing Factors

In his 2005 review of drug-induced hapatotoxicity, Willis Maddrey states that two important factors determine the likelihood of APAP-induced hepatic injury:

- The amount of NAPQI produced by P450 2E1
- The availability of glutathione as a hepatoprotectant.[7]

Factors that affect the amount of NAPQI include the amount of APAP ingested as well as factors that affect the production of cytochrome P450 2E1 and glutathione. Most researchers agree that hepatic glutathione depletion is the critical trigger for APAP hepatotoxicity. Alcohol use can decrease intracellular glutathione and may possibly increase cytochrome P450 2E1 (actual amounts or amounts relative to glutathione). These conditions lead to an overproduction and inadequate inactivation of NAPQI and increase the likelihood of hepatotoxicity. While nonprescription APAP product labels include a warning against use if the consumers has three or more alcoholic beverages in a day, there is ongoing controversy regarding the dose of

acetaminophen and amount of alcohol ingestion needed to predispose a person to liver injury.[4] There are inter-subject, gender, and ethnic differences in APAP metabolism that may influence an individual's susceptability to hepatic injury with use of therapeutic or supratherapeutic doses of APAP. Additional details may be found in Appendix A.

Inter-individual differences in susceptability to APAP-associated hepatic injury

There are inter-subject, gender, and ethnic differences in paracetamol metabolism that may influence an individual's susceptability to hepatic injury with use of therapeutic or supratherapeutic doses of acetaminophen.

- In 1986, Critchley et al studied the 24 hour urinary excretion of acetaminophen and its metabolites in 111 Scottish Caucasians, 67 Ghanese (West Africa), and 20 Kenyans (East Africa). Compared to Caucasians, Africans had a statistically significantly lower recovery of mercapturic acid and cysteine conjugates from the urine, suggesting a reduced metabolic activation of paracetamol (production of NAPQI) (5.2% and 4.5% vs. 9.3%, $p<0.0005$). There was a three fold variation in glucuronide and sulphate conjugation among subjects but a sixty fold variation in metabolic activation of paracetamol.
- In 1992, a study by Patel et al in 125 Caucasians and 33 Asians found no differences between ethnic groups in mean fraction of acetaminophen excreted as glucuronide, but found a bimodal distribution among subjects for extent of glucuronidation and N-acetylation (glutathione-derived conjugates). Critchley et al studied 11 healthy Chinese and nine Caucasians, 21-44 years of age who received a single 20 mg/kg dose of acetaminophen syrup following an overnight fast. They found that Chinese subjects absorbed acetaminophen more rapidly and produced relatively more sulfate conjugates, less glucuronidated conjugates, and less mercaptuic acid and cysteine conjugates. These differences could indicate relative protection against acetaminophen-induced hepatotoxicity for the Chinese individuals compared to Caucasian individuals.
- In 1994, Bock et al randomly selected 194 subjects (98 male, 95 female) to study the impact of gender, oral contraceptive use, smoking, and coffee consumption on the metabolism of acetaminphen. Thirty-eight males and 40 females smoked. The investigators identified a trimodal distribution of subjects: poor metabolizers (8%), extensive metabolizers (11%), and moderate metabolizers (81%). Gender and smoking status significantly affected glucuronidation capacity, which was highest in male smokers and lowest in female nonsmokers.
- In 1994, Whitcomb and Block identified fasting as a risk factor for acetaminophen toxicity based on the depletion of essential cofactors needed for efficient acetaminophen conjugation. Others have studied patients with Gilbert Syndrome who have an inherent defect of UDP-glucuronyltransferase 1A1 (to varying degrees). This genetic variiation leads to decreased APAP glucuronidation and increased production of NAPQI compared to normal subjects. These individuals are believed to have an increased risk of acetaminophen-induced hepatotoxicity.

In 2001, Court et al aimed to characterize inter-individual variability in acetaminophen glucuronidation at a therapeutic serum concentration of drug (0.5 mM) and a supratherapeutic concentration that saturated the glucuronidation mechanism (50 mM). The researchers utilized an in-vitro preparation of human liver microsomes obtained from frozen liver samples. The

study found that hepatic microsomal acetaminophen UDP-glucuronosyltransferase (UGT) activities showed a 15-fold inter-individual variability. At least three different UGT isoforms significantly contributed to and mediated the glucuronidation process and their relative contributions changed based on whether the concentration of acetaminophen. Acetaminophen-UGT activity was about 50% higher in livers from male donors compared to livers from female donors.

The following study findings should be considered:

- Healthy individuals develop elevated transaminases levels at maximum therapeutic doses, at least transiently[67]
- Individuals with decreased oral intake and viral illness may develop hepatic injury or failure at therapeutic or mildly supra-therapeutic doses[68]
- Some individuals who regularly use or abuse alcohol may have a lower threshold for acetaminophen toxicity[69,70]
- In vitro-studies on human liver microsomes suggest inter-individual variability in acetaminophen glucuronidation[71,72]
- In-vitro studies on human hepatocytes suggest that exposure of hepatocytes to acetaminophen with either phenytoin or phenobarbitol leads to decreased glucuronidation. This could lead to increased systemic exposure and toxicity for either or both of these drugs.[73] Previously published clinical data on individuals using acetaminophen and either phenytoin or phenobarbitol have been mixed regarding a decreased threshold for acetaminophen hepatotoxicity.

Some individuals with a potentially lower threshold for APAP-induced hepatotoxicity

Appendix B: Summary of Nourjah et al, 2005.

Six surveillance systems used by FDA's Office of Surveillance and Epidemiology to generate national estimates of acetaminophen-associated overdoses (Nourjah et al, 2005)

In preparation for the September 2002 NDAC, FDA reviewers from the Office of Drug Safety (ODS, now OSE) reviewed acetaminophen-associated hepatotoxicity data from national databases and the FDA Adverse Event Reporting System (AERS) to estimate the public health impact of hepatotoxicity in the United States. Drs. Nourjah, Ahmad, Karwoski, and Willy, reviewers later published a study presenting this data. The authors used six different surveillance systems that included data from emergency departments (EDs), hospital discharges, mortality data, poison control centers, and spontaneous postmarketing adverse drug event reports reported to the Food and Drug Administration (FDA):

- National Hospital Ambulatory Medical Care Survey (NHAMCS)
  - The CDC National Center for Health Statistics conducts this survey annually. The survey includes ambulatory care services in hospital EDs and collects information on: demographics of patients, physicians' diagnoses (up to 3), diagnostic/screening services, procedures, medication therapy, disposition, and causes of injury (where applicable). Uses International Classification of Diseases, 9th revision (ICD-9) coding for diagnoses and the ICD code for injuries and poisonings.

- Consumer Product Safety Commission's National Electronic Injury Surveillance System All Injury Program (NEISS)
  - This database collects data on consumer product-related injuries treated in EDs. A sample of 66 hospitals is annually selected to report injury-related information. Data includes: patient demographics, product(s) involved, intentionality, diagnosis, body part affected, ED disposition, incident locale, fire involvement, and work-related injuries. Since 1973, data is included on drug poisonings in children less than six years of age. Starting in July 2000, data on drug injuries for individuals of all ages are included. To retrieve intentionality data, specific drug product names were used to distinguish prescription and nonprescription acetaminophen products.

- National Hospital Discharge Survey (NHDS).
  - CDC conducts this annual survey to characterize inpatients discharged from non-federal short-stay hospitals in the United States. Data includes estimates of patient demographic characteristics, geographic region of hospitals, conditions diagnosed, surgical and non-surgical procedures performed, days of care and length of stay. ICD-9 coding is used.

- National Multiple Cause of Death File
  - Individual States cooperate with the National Center for Health Statistics to provide statistical information from death certificates. The medical information on death certificates is coded according to World Health Organization rules specified in the ICD. Data includes: demographic, geographic, and cause-of-death information. ICD-9 codes were used to search for intentional and unintentional cases of overdose.

- Toxic Exposure Surveillance System (TESS)
  - TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers in cooperation with more than 60 poison control centers in the United States. Cases included those from the fatal exposures table and the demographic profile of exposure cases table that listed acetaminophen as the primary (first) agent associated with the fatal exposure. Cases were classified as intentional misuse or unintentional overdose.

- FDA Adverse Event Reporting System (AERS)
  - In AERS, the authors conducted a broad search for U.S. cases of hepatic injury reported between 1998 and 2001 with an acetaminophen-containing product as a suspect agent for individuals aged 12 years and older. Cases were excluded if the liver injury was likely attributable to other causes. Cases had to meet one of four predefined case definitions:

    1. non-hospitalized patient with ALT or AST three times the upper limit of normal and total bilirubin at least three times the upper limit of normal or jaundice or INR > 1.5

    2. patient hospitalized or died secondary to an acute liver event.

    The reviewers calculated daily doses based on dosing information provided. If a dose range was provided, the mid-point was used. If the strength of the formulation was unknown, 500 mg strength was used. Cases were categorized as intentional if acetaminophen was used in a suicide attempt or if the patient took a one-time dose of greater than 4 g acetaminophen without a specified indication. Cases were categorized as unintentional if acetaminophen was misused or abused for a therapeutic indication and a suicide attempt was not indicated.

Since each database provided different information in different populations with various degrees of overlap, the results are presented by source. Information from the two databases containing emergency room data is combined.

- ED data (NHAMCS and NEISS):
  From 1993 – 1999, there were an average of 56,000 ED visits per year for APAP-associated overdoses. These visits comprised 7% of all medicinal and biologic substance overdose visits to the ED.
  - 65% of these cases were in individuals between 17 and 64 years of age.
  - 63% of patients were female
  - 56% of were intentional overdoses: 44% suicide attempt, 12% due to use of acetaminophen with other medicines.
  - 23% were unintentional overdoses: 17% accidental ingestions, 6% therapeutic misuse (estimate as based on less than 30 cases)

- Hospital discharges

From 1990 – 1999, there were an average of 26,256 hospitalizations each year for APAP-associated overdoses, which comprised 11% of the total hospital discharges for overdoses with all drugs, medicinal substances, and biologics.

- 74% occurred in individuals between ages 17 and 64 years
- 69% of patients were female
- 74% were intentional overdoses: 33% suicide, 26% APAP and other medicines, 15% suicide and use with other medicinals
- 8% were accidental overdoses that were considered unintentional.

- Mortality files

From 1996 – 1998, there were 1375 deaths (average of 458 per year) identified in which an APAP-associated overdose was either the underlying cause of death or was a contributing cause.

- 1010 records of the 1375 mortality files mentioned suicide or intentional overdose
- 300 records listed the overdose as unintentional
- 65 files indicated unknown intentionality
- 58% of the deceased were females
- 14% were individuals ages 65 years and older
- Among unintentional cases, there was a higher percentage of persons ages 65 years and above (23% vs. 11%)
- Both intentional and unintentional overdoses were more common in females.

- TESS

From 1997 – 2001, there were 112,809 – 119,807 APAP exposures alone or in combination with other products per year. These reports represented about 10% of the 1.2 million pharmaceutical substances exposures reported to TESS each year. During this five year interval, there was little annual variation in number of APAP-associated exposures.

- Of 33,895 APAP exposures in children in 2001, at least 23% involved adult formulations.
- In 2001, nearly 50% of all APAP exposures were unintentional in nature and more than 50% were treated in a health care facility. Two percent of cases involved major effects that were life-threatening or resulted in significant residual disability.
- APAP-associated fatalities represented 16% of the total 1074 fatalities reported to TESS in 2001. About 50% of these fatalities occurred in individuals using a single-ingredient nonprescription APAP product. Ten percent involved multiple APAP products ingested simultaneously.
- In 2001, there were 173 APAP-associated fatalities – almost twice the number of deaths reported to TESS in 1997 (N = 98). Intentional fatalities and unintentional fatalities accounted for 55% and 26% of the total fatalities respectively.

- AERS

From 1998 – 2001, FDA received 759 domestic reports of hepatotoxicity associated with the use of APAP-containing products in individuals ages 12 years and older. Four hundred seventy-eight reports met inclusion criteria, and 70% of these reports were about women. Two hundred (42%) cases or reported hepatotoxicity followed an apparent suicide act, whereas 198 (41%) events appeared unintentional. Among 103 (52% of 278) reports that provided information with which to estimate the daily APAP dose (g/day), 73 (70%) reports suggested that the subject took

more than the maximum recommended APAP dose of 4 g/day. Thirty reports of unintentional overdose with dosing information involved apparent APAP doses of 4 g/day or less.

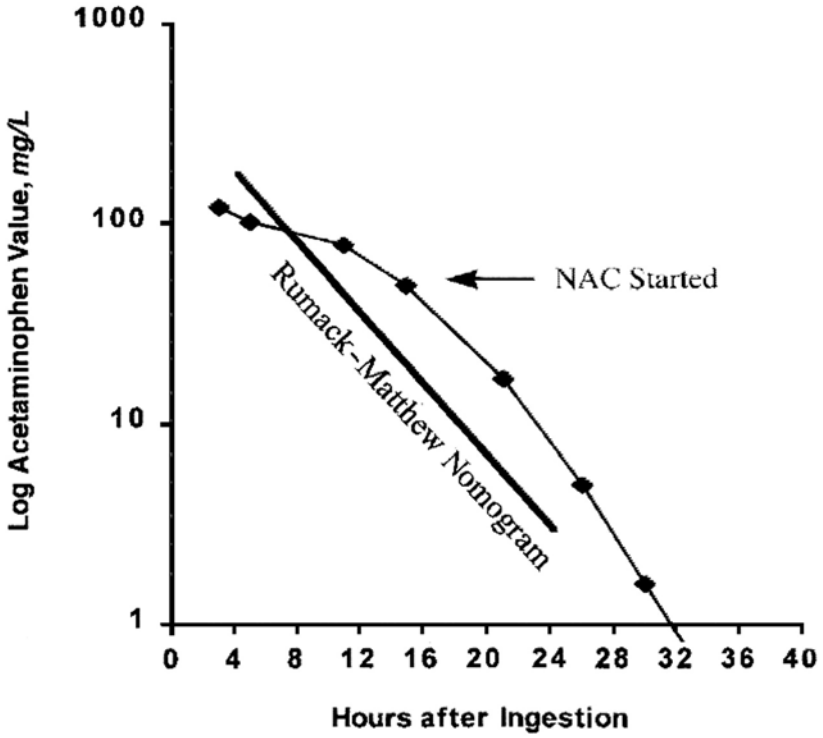
Among the 198 unintentional overdose cases, 170 (86%) reports indicated APAP use for a therapeutic indication, primarily analgesia. The remaining 28 reports involved abuse or misuse of an APAP-containing product, unspecified medication error, or unlabeled use. Among the 170 reports with APAP used for a therapeutic indication, 89 had dosing information with a suggested mean daily dose of 7.5 g. Forty-four reports included noted use of alcohol and 29 cases had a prior history of liver disease. These two subgroups had a mean daily dose of 6.1 g/day and 6.3 g/day respectively. Use of a formulation containing 500 mg of APAP was reported twice as often as use with a 325 mg formulation, and 28% of the 198 unintentional overdose reports suggested use of more than one APAP product – often an OTC product with a prescription product.

The authors acknowledged the following limitations of their database-acquired information:

- Definitions and methodology used to identify cases of APAP-associated overdose and intentionality were different for different databases
- They were unable to review medical records to verify diagnosis and intent
- The time periods of study for each database were inconsistent
- Analyses of data from the databases were limited because of missing information on possible risk factors, details on the consequences of the overdoses (like whether there was liver failure), and missed cases due to attribution errors by healthcare providers.

Despite these limitations, the authors concluded that the large numbers of APAP-associated overdoses identified in national databases suggest misuse or abuse of APAP in the United States population. They acknowledged that certain factors, like concurrent liver disease or alcohol use, may lower the threshold dose of APAP-associated toxicity and measures to reduce the number of APAP-associated overdoses, particularly those due to unintentional misuse, should be considered.

Appendix C:
Application of the Rumack-Matthew nomogram for treating acetaminophen toxicity in a particular case.



Vassalo S, Khan A and Howland MA. Use of the Rumack-Matthew nomogram in cases of extended-release acetaminophen toxicity. Ann Int Med 1996; 125: p.940

Appendix D:
Concepts for PSA's and Other Educational Messages About the Safe Use of OTC Pain and Fever Medicines

- **Title:** Baby Medicine is Not Like Baby Shampoo
  Target Audience: Parents and child care providers

  Message:

  Baby medicine is not like baby shampoo.

  It is not weaker
  It is not gentler
  It is just smaller in size

  Your baby's medicine allows you to give your baby the right amount of medicine based on how much your baby weighs.

  The medicine for your older child does the same.

  More weight, more medicine.
  The right amount based on the size of your child.

  How perfect.

  …Know your child's weight.

- **Title:** Real Men Don't Ask For Directions
  Target Audience: Adolescent boys and men

  Message:

  When it comes to medicines…..asking for directions is cool

  Every over-the-counter medicine label has directions to help you get where you are going – a place where you feel better.

  Follow the directions on your medicine's label. If you don't get to "feeling better" then STOP. Ask for help.

  Maybe you are driving down the wrong road. Your doctor or pharmacist can help you find the medicine that is right for you and your problem.

- **Title:** Get intimate with your pain and fever medicine
  Target audience: All consumers who use OTC pain and fever medicines

  Message:

  How well do you know your pain and fever medicine?

  Not well enough to ignore the directions and warnings.

  No matter how many times you use your pain and fever medicine, it can still hurt you if you use too much.

  Using more acetaminophen than recommended can damage your liver.
  Using more ibuprofen or naproxen sodium than recommended can damage your kidneys.

  Be Smart:

  - Know the active ingredient in your medicine
  - Read the warnings to see if the medicine is right for you and your problem
  - Use the right dose at the right time
  - Measure liquid medicines with a medicine measuring tool
  - If the medicine is not helping you, don't take more. Talk to a healthcare professional about what to do next.

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Assessment of the Analgesic Efficacy and Hepatotoxicity of Opioid/Acetaminophen Combination Products

March 12, 2007

Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
US Food and Drug Administration

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Acetaminophen-related hepatotoxicity is a well-known phenomenon. As a percentage of all acute liver failure cases, overdose due to acetaminophen, both in over-the-counter (OTC) products and prescription (Rx) products, has increased from 28% in 1998 to 51% in 2003.

This review provides an evaluation of the available data on the analgesic efficacy of the acetaminophen (APAP) component of opioid/APAP combination products, the hepatotoxicity related to the APAP component in the products, as well as prescription patterns (which clinical specialties are prescribing the products and for which indications). Options are presented with respect to potential regulatory actions that could be pursued regarding these combination products.

All opioid/APAP combination products on the U.S. market, except for tramadol/APAP combination (Ultracet®), were approved for *the relief of moderate to moderately severe pain.* Ultracet® is approved for the short-term management of acute pain, with therapy limited to no more than 5 days. Recently published guidelines by the American Pain Society for the management of pain due to malignancies (in 2005) and by the American Society of Interventional Pain Physicians for chronic pain due to other etiologies (in 2006), and the profile of dispensed prescriptions from Verispan Vector One databases, indicate that opioid/APAP combination products are being extensively prescribed for both acute and chronic pain, including pain due to malignancies and pain due to other diagnoses, such as post-surgical pain, back pain, or joint pain (including osteoarthritis). Hydrocodone/APAP combination products are the most commonly prescribed opioid analgesic.

There are only a few reports in the medical literature that assess the analgesic efficacy of opioid/APAP combination products, particularly with factorial design studies that would evaluate the analgesic superiority of the combination over its individual components. Only four full-factorial design studies have been identified: one each of hydrocodone/APAP and oxycodone/APAP and two of codeine/APAP. There were more than 30 partial-factorial design studies of codeine and propoxyphene with APAP. All of these studies were conducted in acute pain populations comparing the combination with only one of the individual components; none were conducted in a patient population experiencing chronic pain.

According to the 2005 report from the U.S. Acute Live Failure Study Group, the opioid/APAP combination products significantly contributed to APAP overdose and hepatotoxicity, particularly the hydrocodone/APAP combination. The number of opioid/APAP-related acute liver failure cases identified by this study group was similar to the number of cases associated with OTC APAP products. The majority of the opioid/APAP-related acute liver failure cases were due to unintentional APAP overdose. It is unknown if the opioid/APAP-related APAP overdose cases were associated with the development of tolerance to and dependence on the opioid component of the combination products.

The Office of Surveillance and Epidemiology (OSE) has performed analyses of various post-marketing surveillance databases and has found data suggesting that use of the opioid/APAP combination products are implicated in APAP overdose, hepatotoxicity and/or death. However, the databases were unable to determine the potential role of opioid dependence and tolerance on the observed toxicities.

Synthesis of the information available from product utilization databases and treatment guideline publications, the available evidence on the efficacy of the combination products in the literature, reports from study groups like the U.S. Acute Liver Failure Study Group, and the post-marketing surveillance databases, has resulted in the following conclusions:

1. Opioid/APAP combination products are extensively prescribed for both, acute to chronic pain, due to a variety of pathological processes.

2. There is a suggestion in the literature that APAP in combination with codeine, hydrocodone or oxycodone, but not propoxyphene, results in analgesic superiority to the individual components for acute pain. However, the strength of the data to support an overall conclusion on the utility of the combination products is limited due the fact that the designs of the studies were suboptimal and chronic pain models have not been evaluated.

3. Opioid/APAP combination products clearly play a role in both intentional and unintentional APAP overdoses and related hepatotoxicity. However, it is not clear what role the development of tolerance to and/or physical dependence upon the opioid component in the combination products plays in these cases.

When all these factors are taken together, it is difficult to conclude with certainty that the overall benefit of combining acetaminophen with opioids in fixed-dose combination products outweighs the risk.

The following options are some of the possible strategies that may be able to address this concern. The options are listed in the order of increasing complexity; they are not mutually exclusive since it is likely that any successful strategy will require a multi-faceted approach.

1. ***Educational outreach***
   The majority of the opioid/APAP-related acute liver failure cases reported by the Acute Liver Failure Study Group were due to unintentional APAP overdose. Some of the cases reported the use of multiple APAP-containing products, including concomitant OTC preparations. Increased awareness of APAP content in products by both health care professionals and patients is needed and such educational efforts may reduce the possibility APAP overdose. Advertisements in the traditional media (television, radio, and periodicals), as well as educational activities through the internet, professional conferences, or continuing medical education (CME) activities, may be useful.

It is noted that previous outreach programs have been conducted and they have had variable success. However, there are new methods such as the FDA information sheets which may make additional efforts worthwhile. However, it should be acknowledged that an educational approach alone is not enough. It will need to be combined with whatever other strategies are implemented and, conversely, any other strategy will have a greater chance of success if it is combined with an educational outreach component that brings attention to and explains the purpose of that particular strategy.

2. ***Labeling modification***
   The package insert of all opioid/APAP combination products may be modified to include a boxed warning to increase awareness by the health care professionals (who will then, theoretically also inform patients).

3. ***Medication guide***
   The creation of a medication guide may reduce the potential for APAP overdose from multiple products by increasing the likelihood that the information is being conveyed to patients.

   As it has been reported that the majority of the unintentional overdoses have been due to patients taking multiple APAP-containing products, both OTC-preparations and prescription products, a medication guide could be strong a counterpart to the educational outreach efforts that are ongoing with the OTC products.

4. ***Reduction of the amount of APAP in the combination***
   Reformulation of the combination products so that the APAP component is only 325 mg (from the current 750 mg that can be found in certain formulations) may reduce the risk of unintentional overdose.

5. ***Uncoupling the components of the opioid/APAP combination products***
   Reformulation of the combination products so that the APAP component is completely eliminated will avoid APAP-related toxicities and overdoses associated with the fixed-dose combinations. However, the 4 most commonly prescribed opioid products are APAP combination products. Whether this is due to prescriber familiarity with these products, patient preference, convenience due to their Controlled Substances Act scheduling designation, or other reasons is unclear.

   It is worth noting that, per the CDER Orange Book, there are currently no approved single entity products for codeine on the U.S. market. Hydrocodone-only products available in the U.S. are formulated with a low dose of homatropine (to discourage deliberate overdosage) but are not indicated for analgesia. These products are approved for the symptomatic relief of cough, and are classified as Schedule III. Another single entity opioid product is propoxyphene, marketed in U.S. as an analgesic; it is a Schedule IV product, but it constitutes less than 5% of the prescriptions dispensed.

Although there are several approved single-entity opioid oral products (oycodone, hydromorphone, oxymorphone, fentanyl, and morphine), they may not be adequate substitutions for a patient whose pain management has been stable on the combination products for several reasons. Theses products differ from the combination products in potency, safety and tolerability profiles, and schedule designation.

There are few alternative products for physicians to prescribe under Schedule III. Codeine combinations with acetaminophen or aspirin are not as frequently prescribed as hydrocodone combination products, perhaps due to a perception of decreased efficacy and more adverse events, although there are little data to quantify these effects. Although morphine products in combination would be prescribed under Schedule III, currently there aren't any morphine combination products approved in the U.S.

Analgesics that are classified as Schedule IV, such as butorphanol, dextropropoxyphene and pentazocine, as well as unscheduled products, such as tramadol, are generally recognized to be less effective for moderate to severe pain than hydrocodone and the opioids prescribed classified as Schedule II.

Aside from the issue of needing to see their prescribers more often in order to get prescription refills which, although it may appear as a minor inconvenience, may actually be a major impediment for some patients, it is likely that that removal of these combination products will have some patients turning to other products. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally not sufficient for acute postoperative pain, however, they are considered as the first step in analgesic therapy for chronic pain, to be followed by opioids, alone or in combination, once greater analgesia is required. Hydrocodone/ibuprofen and hydrocodone/aspirin combination products are available under Schedule III, but they, like the NSAIDs, each have their own safety issues.

Therefore, reformulation of the opioid/APAP combination products to remove the acetaminophen will significantly impact the pain management options for those patients who have been, or may be, well-managed with opioid/APAP combination products.

BACKGROUND

Acetaminophen (APAP)-related hepatotoxicity is well known and the percentage of the reports of acute liver failure associated with an overdose of an APAP-containing product, both over the counter (OTC) and prescription (Rx) formulations, has increased from 28% in 1998 to 51% in 2003. Opioid/APAP combination products, the only prescription APAP products on U.S. market, have been the source of increased concern after the U.S. Acute Liver Failure Study Group reported their findings in 2005 that more than 50% of APAP-related acute liver failure cases were related to opioid/APAP combination products.

This review provides an evaluation of the role of opioid/APAP combination products in pain management, an assessment of the available data on the analgesic effects of the combination compared to its individual components, a summary of the APAP-related hepatotoxicity associated with the opioid/APAP combination products, and options for potential regulatory actions that could be pursued regarding these combination products.

PAIN MANAGEMENT PRACTICES

Role of Opioid/APAP Combination in Pain Management

Approved Indication

Except for the tramadol/APAP (Ultracet®) combination product, all opioid/APAP combination products have been approved for *the relief of moderate to moderately severe pain,* with the dosing recommendations limiting the maximum APAP dose to 4 grams per 24 hours. These combinations products have been used for pharmacologic management of acute pain and chronic pain, including cancer and non-cancer pain. Ultracet® was approved for the short-term (≤ 5 days) management of acute pain.

Clinical Practice

In the *Guideline for the Management of Cancer Pain in Adults and Children* (published by the American Pain Society in 2005)[i], APAP combinations with hydrocodone, codeine, or oxycodone are recommended for the management of mild to moderate persistent pain due to cancer in adults and children. According to the guidelines, there was strong evidence for the use of opioid analgesics to treat cancer pain on an around-the-clock basis and/or as-needed base; however, the guidelines did not address the strength and consistency of the data to support the use of opioid/APAP combination products for this indication.

For the patient with chronic pain due to a non-cancer etiology, there is little solid evidence in the literature to support the use of opioid combination with APAP. As per the *Opioid Guidelines in the Management of Chronic Non-Cancer Pain*[1], as many as 90% of patients in pain management settings have been reported to receive opioids for chronic

[i] Miaskowski c et al: American Pain Society (APS) 2005, 166p (Clinical Practice Guideline, No. 3), http://www.ampainsoc.org/

pain. Hydrocodone combinations with acetaminophen or ibuprofen were the most commonly used opioid analgesic for treatment of chronic pain. However, the strength of available evidence from the literature to support opioid use for chronic pain was *Limited, Level IV*. Although the guideline did not make particular recommendations on individual opioid analgesics for chronic pain, the *Ten Step Process: An Algorithmic Approach for Long-Term Opioid Therapy in Chronic Pain* was recommended, which includes a comprehensive initial evaluation and diagnosis, risk-benefit assessment, dose adjustment, and monitoring for adverse reaction and abuse.

Pharmacological Rationale

Pharmacologically, opioids and APAP mediate analgesic effects through different mechanisms of action. Opioid analgesics are μ-opiate receptor agonists that work through changes in the perception of pain at the spinal cord and, through higher centers in the central nervous system, an alteration of the emotional response to painful stimuli.[2] APAP is also considered a centrally acting analgesic, although its mechanism of action is not completely clear. Recent studies suggest that APAP selectively inhibits the peroxidase active site of COX-1 and COX-2 (prostaglandin H2 synthases 1 and 2) in neurons and vascular endothelial cells but not in platelets and inflammatory cells.[3] This cellular selectivity of COX inhibition results in analgesic and antipyretic effects for APAP with little anti-platelet and anti-inflammatory activities.

Several review articles discuss the *pharmacological* rationale of the analgesic combination[4-7]. The combination of opioids with APAP may have the following advantages for the treatment of pain:

- Increased analgesic effects: additive or synergetic analgesic effects through a combination of actions that relieve pain by different pharmacological mechanisms.
- Decreased adverse reactions: lower doses of individual components in the combination which may reduce dose-dependent adverse drug reactions (incidence and/or severity).
- Increased compliance: the convenience of taking the combination products (reduced the number of pills and simplified dosing schedule).

However, there is limited clinical evidence in the literature to support the above rationales. There were no efficacy and safety data submitted for review during the approval process of any of the opioid/APAP combination products, except for tramadol/APAP (Ultracet®, NDA 21-123, approved in 2001), due to historical precedence and the different requirements of the 505(j) application process.

Usage of Opioid/APAP Combination Products

Currently, there are approximately 250 approved opioid/APAP combination products marketed in the U.S., as listed in Appendix #1. The hydrocodone/APAP combinations are at the top of the list (n=106 products), followed by oxycodone/APAP (n=44), codeine/APAP (n=40) and propoxyphene/APAP (n=22). The majority of these opioid/APAP combination products were approved under the ANDA (n=247) regulations,

with only four being approved as NDAs. Among the four NDA products, the propoxyphene/APAP combination was approved prior to January 1, 1982 (NDA 17-122), the pentazocine/APAP combination was approved on September 23, 1982 (NDA 18-415), the codeine/APAP/butalbital/caffeine combination was approved on July 30, 1992 (NDA 20-232) and tramadol/APAP (Ultracet®) was approved on August 15, 2001 (the product was assessed with factorial design studies).

The utilization data for the opioid/APAP combination products in U.S. and their indication for use were reviewed by OSE in 2005[ii], 2006[iii] and 2007[iv], as summarized below and Appendices #2 and #3 (also see the OSE reviews for details).

Market Share of Rx vs. OTC APAP products (Appendix #2):
The total sales of APAP products increased from 24.5 billion extended units (tablets/capsules/milliliters of solution) in 2001 to 28.5 billion in 2005 (increased by 17%). Of these, the majority of APAP products were sold as OTC (67% - 61%, slight decrease annually over the four years). The market share of Rx products (opioid/APAP combination) had a slight increase in the yearly proportion from 2001 (33%) to 2005 (39%). The overall sales of opioid/APAP combination products have increased by approximately 38% from an estimated 7.9 million extended units in 2001 to 11 million in 2005. The sales of hydrocodone/APAP combination products nearly doubled from 2001 to 2005 and accounted for 51% in 2001 and 60% in 2005 of the opioid/APAP product market.

Dispensed Rx of opioids vs. opioid/APAP combinations (Appendix #3):
The four most commonly dispensed outpatient prescriptions of opioid analgesics from 2000 to 2005 are hydrocodone, oxycodone, propoxyphene and codeine. The majority of the opioid prescriptions were dispensed as APAP combination: >98% of the hydrocodone, 68-70% of the oxycodone, 96% of the propoxyphene, and 71-76% of the codeine prescriptions.

The number of dispensed prescriptions increased from 2000 to 2005 by 21% in all of the opioid/APAP combination products (14.3 to 17.3 billion units) and by 39% on hydrocodone/APAP combination products (7.5 to 10.4 billion units). Hydrocodone/APAP combination products have been at the top of list since 1997[iii], and in the past 5 years the market share has increased from 53% in 2000 to 60% in 2005. Based of the dispensed prescription data from 2000-2005, the market shares for the other combination products were: oxycodone/APAP increased from 12% to 14%, propoxyphene/APAP decreased from 20% to 13%, and codeine/APAP decreased from 16% to 9%.

[ii] Gita Akhavan-Toyserkani: Postmarketing Safety Review of Hydrocodone Combination (Drug abuse, Dependence, Withdrawal, Overdose, Suicide and Death), OSE Review, Dec 20, 2005
[iii] Laura Governale: OTC and Prescription Combination APAP use. OSE Review, Nov 30, 2006
[iv] Kendra Worthy: Drug Use Review of Acetaminophen (APAP)/Hydrocodone. OSE Review, Jan 23, 2007

Prescription by Patient Age (Appendix #4):
The majority of the dispensed prescriptions for opioid/APAP combination products were for adult, age 17 and above, from 2002 to 2005; the highest counts are for patients between the ages of 41-50 years.

Prescription by Medical Specialty (Appendix #5):
The clinical specialties that prescribed the most opioid/APAP combinations were general practice, internal medicine, dentistry, and orthopedic surgery.

Prescription by Diagnosis (Appendix #6):
Based on the database of Physician Office-Based Practice, the most common diagnoses prescribed hydrocodone/APAP, oxycodone/APAP, and codeine/APAP from 2002 to 2005 were post-surgery follow-up, backache, lumbago and osteoarthrosis.

EFFICACY OF THE OPIOID/APAP COMBINATION

Analgesic Efficacy in Acute Pain

All opioid/APAP combination products, except tramadol/APAP combination (Ultracet®, NDA 21-123), were approved under 505(j) application (ANDA) regulations (see Appendix #1 for list of currently-marketed products in the U.S.). Therefore, no additional efficacy data were submitted to support the superior analgesic effects of the combination compared to its individual components.

Well-controlled data to demonstrate the analgesic superiority of the combination are limited. After an extensive literature search of different databases, a total of four full-factorial design studies (all in acute pain population) were identified: one of hydrocodone/APAP, one of oxycodone/APAP and two of codeine/APAP. There are also a few partial-factorial design studies, which mostly compared the combinations with APAP alone. Overall, the literature suggests that the codeine/APAP combination results in additive analgesia compared to the individual components. However, there is limited evidence in the literature to support the analgesic superiority of APAP combinations with hydrocodone or oxycodone over the individual components.

The following is a brief summary of those factorial design studies. The detailed reviews of the full-factorial design studies and two partial-factorial design studies can been found in Appendix #7. Literature summaries of efficacy studies on opioid/APAP combination products are tabulated in Appendix #8 (hydrocodone/APAP), Appendix #9 (oxycodone/APAP) and Appendix #10 (codeine/APAP).

Factorial design study of hydrocodone/APAP combination
This was a randomized, double-blind, placebo-controlled, full-factorial design study in postpartum patients[8] (See Appendix #7-1 for details). The patients received a single oral

dose of hydrocodone/APAP (10/1000 mg) combination (n=21), hydrocodone (10 mg) alone (n=22), APAP (1000 mg) alone (n=22) or placebo (n=22) followed by 6-hour pain assessment. All treatments were statistically superior to placebo in analgesia outcome measures. Although patients treated with the combination product experienced "additive" pain relief in terms of half-pain relief (with statistical significance versus hydrocodone or APAP alone), the results were not supported by the pain intensity change from baseline and pain relief score.

Factorial design study of oxycodone/APAP combination

One full-factorial design study was published by Cooper, et al, in 1980[9]. It was a randomized, double-blind, 6-arm, single-dose study in post-operative dental pain patients. The patients (37-45 per arm) were treated with oxycodone/APAP combinations (5/500 mg, 5/1000 mg or 10/1000 mg), oxycodone (5 mg), APAP (500 mg) or placebo, followed by a 4-hour analgesic assessment of the following endpoints: pain intensity (PI) and pain relief (PR). All active treatment groups were superior to placebo, per the authors, but statistical significance was not reported. APAP/OX (500/5 mg) in combination was superior to OX (5 mg) or APAP (500 mg) in PI time-course, PR time-course, the sum of pain intensity difference (SPID), 4-hour total pain relief (TOTPAR4), peak PR, time to re-medication, and global impression; however, the statistical significance of the superiority was not reported. There was a trend of a dose-response in pain measures among different combinations with APAP (500-1000 mg) and OX (5-10 mg), but no statistical significance. (See Appendix #7-2 for details).

A partial-factorial design was published in 1996. It was a randomized, double-blind, single-dose study in patients with pain due to abdominal or gynecological surgery [10]. The patients (n=30 per arm) received a single-dose treatment of oxycodone/APAP (10/650 mg), immediate-release oxycodone (15 mg), controlled-release oxycodone (10, 20, or 30 mg) or placebo with a 12-hour post-dosing pain assessment. All active treatments were statistically superior to placebo. Oxycodone/APAP (10/650 mg) in combination tended to be superior to immediate-release oxycodone (15 mg) in PI time-course, PR time-course, SPID, and TOTPAR6, with unreported statistical significance. (See Appendix #7-3 for details).

A meta-analysis published in Cochrane Systemic Review Database pooled efficacy data from seven randomized controlled single-dose trials in acute postoperative pain[11], including the two factorial design trials discussed above[9, 10] ; the remaining five trials used comparisons to placebo. By using descriptor (number-needed-to-treat (NNT) for >50% pain relief) and relative benefit converted from the number of patients with ≥ 50% maxTOTPAR in each trial, the oxycodone/APAP (5/325, 5/500 or 5/1000 mg) combination was superior to placebo. The relative benefit of oxycodone 5 mg over placebo estimated from the Cooper's trial[9] was 1.0 (95% CI: 0.5-2.0), suggesting that addition of APAP to oxycodone 5 mg may result in an additive analgesic effect. However, a firm conclusion would require more studies, particularly in full-factorial design.

Factorial design study of codeine/APAP combination

There were two full-factorial design studies found in the literature[12, 13]. Both were randomized, double-blind, single-dose studies in patients with post-surgical pain. One was in 116 patients with orthopedic or general surgery[13], comparing the analgesic effects of codeine/APAP (60/1000 mg, n=45) with codeine (60 mg, n=23) or APAP (1000 mg, n=45); the other studied 90 male patients after meniscectomy[12], comparing the analgesic effects of codeine/APAP (60/1000 mg) with codeine (60 mg), APAP (1000 mg) or placebo. Overall, the codeine/APAP combination was statistically superior in analgesic effects to codeine but not to APAP in both studies.

The partial-factorial design studies compared the combination with APAP, and lacked a codeine arm, as tabulated in Appendix 10. The codeine/APAP combination showed superiority to APAP (at the same dose) in single-dose acute pain trials. A meta-analysis published in 1997 pooled 13 randomized controlled trials[14] using the number-needed-to-treated (NNT) for ≥50% pain relief as descriptor of analgesic effect across trials and showed additional pain relief with the codeine/APAP combination as compared to APAP. In the same analysis, the authors generated NNT values for codeine 60 mg from other post-operative acute pain trials (with single-patient meta-analysis), which suggests that codeine/APAP combination was superior to APAP or codeine at the same dose in NNT for ≥50% pain relief, without overlapping 95% CI (see Appendix 7-6 for details).

Baseline pain intensity seems to play an important role in determining the sensitivity of analgesic effects in post-operative pain trials. In a randomized placebo-controlled single-dose study in patients with pain due to Caesarean section[15], the additive analgesic effects of the codeine/APAP (60/1000 mg) combination compared to APAP (800 mg) was shown only in patients with severe baseline pain (VAS >60 mm) but not in patients with moderate baseline pain (VAS=40-60 mm). This may explain why the codeine/APAP combination did not show superiority to APAP in the two full-factorial design studies. In these two studies[12, 13] the baseline pain intensity of patients was less than severe (VAS < 60 mm or < 3 on 5-point scale).

Factorial design study of other opioid /APAP combinations

Except for Ultracet® (tramadol 37.5 mg/APAP 325 mg combination, NDA 21-123), all remaining opioid/APAP combination products, including propoxyphene/APAP and pentazocine/APAP combination, were not assessed with full-factorial design studies to support their superior analgesic effects over the individual components at the same dose. There were two meta-analyses with different data processing approaches pooling data from 11 trials in one article[16, 17], and 26 trials in the other[18], on propoxyphene/APAP combination products. All trials were in acute pain and of a randomized controlled design comparing a single-dose of the combination to placebo and/or APAP but not propoxyphene; these were published prior to 1997. It was concluded from both meta-analyses that propoxyphene/APAP combination had no superior analgesic effects over propoxyphene or APAP.

Non-factorial design study of opioid/APAP combinations

There are many randomized controlled studies in the literature that compare the analgesic effects of hydrocodone/APAP combination against placebo in patients with acute pain (see overall summary in Appendix #8). Although an active comparator was included in most studies, neither hydrocodone alone nor APAP alone was studied. The study population was patients with acute pain, such as post-surgical dental pain[19, 20], orthopedic surgery[21-23], sprain[24], or other surgical procedure[25]. Although the results from these studies, which were mostly single oral dose studies, indicate that hydrocodone/APAP combination was superior over placebo for relieving acute pain, it is impossible to conclude that there were any additive analgesic effects of the combination. The tested dose strengths of hydrocodone/APAP combination in the studies were 5/325 mg, 7.5/500 mg, 7.5/650 mg, 7.5/750 mg, 10/650 mg, or 10/100 mg. While 325 – 650 mg APAP is in the lower end of therapeutic level (the generally-accepted therapeutic dose of APAP is 1000 mg), it is undistinguishable if the analgesic superiority demonstrated by the combination was contributed by 5 – 10 mg of hydrocodone. There are no randomized placebo-controlled studies in the literature to demonstrate the analgesic efficacy of a single hydrocodone entity at any dose levels except the above factorial design study[8]. In the Hydrocodone Monograph posted on the Clinical Pharmacology online database[v], the recommended therapeutic dose of hydrocodone for pain relief in adults is 5 – 10 mg every 4 – 6 hours as needed, suggesting that the 5 or 10 mg hydrocodone in the APAP combination may contribute the analgesic effects of the combination.

Analgesic Efficacy in Chronic Pain

The analgesic effects of the opioid/APAP combination in patients with chronic pain have been much less studied. There were no factorial design studies identified in the literature to assess the analgesic superiority of opioid/APAP combination over the individual components in any chronic pain patient population. Randomized controlled studies of opioids for chronic pain in the literature mostly focus on opioid single-entity products other than opioid/APAP combination and only a few studies included a treatment arm of opioid/APAP combination products. Most of these studies were discussed in published systematic reviews in 2004[26] and 2005[27] or meta-analyses in 2006[28] and 2007[29]. However, the evidence level from these studies to support opioids for management of chronic pain is "Limited", as concluded in the *Opioid Guidelines in the Management of Chronic Non-Cancer Pain*[1].

In a meta-analysis[28], 28 randomized placebo-controlled trials of opioids for chronic non-cancer pain (OA, RA, back pain, neuropathic pain or fibromyalgia) were identified. The five opioid analgesics studied in these trials were codeine, oxycodone, propoxyphene, morphine and tramadol. The meta-analysis showed that opioids were more effective than placebo both in pain relief and functional outcome. However, the average duration of treatment was 5 weeks, and mostly ≤ 4 weeks, which is too short to assess analgesic effects in chronic pain. Dropout rates averaged 33% in the opioid treatment group and

[v] Hydrocodone monograph: Clinical Pharmacology online http://www.clinicalpharmacology-ip.com

38% in the placebo control across all studies; the handling of missing data due to dropouts was not specified.

Two studies included in this meta-analysis contained a treatment arm of an opioid/APAP combination. The first was a placebo-controlled 4-week study comparing oxycodone/APAP (5/325 mg) with oxycodone controlled-release (CR, 10 mg) in patients with severe pain due to osteoarthritis.[30] All patients entered a 30-day open-label titration period with oxycodone (immediate release, 5 mg qid) immediately before being randomized to oxycodone/APAP, oxycodone-CR, or placebo. The oxycodone/APAP was superior to placebo in the improvement of pain intensity and sleep quality and comparable to oxycodone-CR at 2 and 4 weeks. However, the study's results were confounded by several factors, such as subjects continuing NSAID therapy during the study and an open-label oxycodone-IR titration period prior to randomization that did not contain a washout period (see Appendix 7-7 for detail).

The second opioid/APAP combination study included in this meta-analysis was a one-week placebo-controlled study of codeine/APAP (30/500 mg) in rheumatoid arthritis patients with moderate-to-severe pain (n=20/arm)[31]. The codeine/APAP combination was statistically superior to placebo in the pain intensity reduced at each time-point and in the 7-day SPID.

In another meta-analysis published this year, 15 studies on opioid treatment for chronic back pain were reviewed[29]. Two of the studies were one-week comparisons between caffeine/APAP (50/500 mg) and propoxyphene/APAP (30/400 mg)[32] and between codeine/APAP (30/500 mg) and tramadol (50 mg)[33]. The analyses did not show pain improvement in favor of the opioid treatment group compared with placebo or a non-opioid control. The authors also pointed out limitations on these studies, including publication bias, poor study quality, and short duration of treatment.

SAFETY OF THE OPIOID/APAP COMBINATION

Hepatotoxicity

APAP in the opioid/APAP combination product has at least the same hepatotoxic profile as APAP single-entity products. There is no clinical evidence to suggest that the opioid in the combination increases the hepatotoxic effects of APAP. However, opioid/APAP combination products, particularly the hydrocodone/APAP combination, contributed approximately half of the acute liver failure cases reported from 22 study centers in the U.S. between 1998 and 2003; most of them were related to unintentional APAP overdose. Since the total use of the prescription opioid/APAP combination products is likely less than APAP products marketed OTC, the incidence of acute liver failure related to opioid/APAP combination products may be much higher.

Drug-Drug Interactions: There are limited data in the literature to evaluate the pharmacokinetic and pharmacodynamic drug-drug interactions between opioids and APAP. Several studies in animals have demonstrated that peripheral or central (intracerebroventricular) administration of morphine, hydromorphone or propoxyphene depletes hepatocellular glutathione[34-38], presumably through stimulation of central μ-opiate receptors. Although hydrocodone was not administered in those studies, its active metabolite, hydromorphone, did have an effect on hepatic glutathione. The mechanism of central effects suggests that depletion of hepatic glutathione is a class effect of opioids. Glutathione is a key factor in the detoxification of NAPQI, (N-acetyl-p-benzoquinone imine), a hepatotoxic metabolite of APAP. Therefore, glutathione depletion by opioids may enhance the APAP-induced hepatotoxicity or decrease the hepatic threshold to APAP toxicity. Interestingly, one other animal study demonstrated that repeated exposure to incremental dose of APAP in mice up-regulated glutathione level and down-regulated hepatic CYP2E1 and CYP1A2 with 4-fold increase in LD50 in response to subsequent lethal dose of APAP[39]. This study suggests that chronic exposure of APAP from opioid combination may attenuate the opioid-induced hepatic glutathione depletion. However, the clinical susceptibility to APAP-associated hepatotoxicity from APAP-opioid as opposed to APAP alone in humans is unknown.

Hepatotoxicity study in healthy subjects

A recently published study (sponsored by Purdue Pharma LP) demonstrated that 1000 mg of APAP in the opioid combination administered every 6 hours for 14 days significantly increased serum ALT in healthy subjects, though the ALT elevation seems comparable to that from APAP alone.[40] The study was a randomized, single-blind, placebo-controlled design to assess the hepatotoxicity of the following four treatment groups: APAP combination with oxycodone, hydromorphone or morphine, and APAP alone. The frequency and magnitude in elevated ALT was comparable across all of the active comparators, suggesting that the opioid component does not increase the hepatotoxicity (at least from the ALT elevation perspective) of the APAP in the combination.

Hydrocodone/APAP combination was not evaluated in the above study but was included in an unpublished study (Study Protocol HXA1017) conducted by the same sponsor (Purdue Pharma LP), and which was submitted to IND 55,965 to support a triple combination product, Hydrocodone/Naltrexone/Acetaminophen (HXA) tablets. In this study healthy adult subjects (n=29/arm) were treated with 2 tablets (1000 mg APAP) of Vicodin (hydrocodone/APAP 5/500 mg), Vicodin/Naltrexone, HXA (5/0.125/500 mg) or placebo every 6 hours for 14 days. Elevations in ALT (>3x ULN) during the study occurred in 45% subjects on Vicodin, 21% on Vicodin/Naltrexone, 17% on HXA and 3% on placebo (see Appendix #11 for details). The IND was later inactivated due to the significant hepatotoxicity.

APAP-related Acute Liver Failure

According to the report by the Acute Liver Failure Study Group in 2005 [41] , 275 (42%) of 662 confirmed acute liver failure (ALF) cases collected from 22 U.S. academic medical centers over a 6-year period (between January 1, 1998 and December 31, 2003) were related to APAP overdose (see Appendix #12 for details). Opioid/APAP combination

products, mostly hydrocodone/APAP, were the major contributors. The majority (69%) of cases of unintentional overdose were due to an overdose of hydrocodone/APAP products.

Among the 275 APAP-related ALF cases:

- 48% (n=131) reported an unintentional overdose
- 44% (n=122) were intentional (suicidal)
- 44% (n=120) took prescription APAP/narcotic combination products
    - 69% (83 of 120) were hydrocodone/APAP combination
    - 63% (83 of 131) were unintentional
    - 18% (22 of 122) were intentional

The report defined *"unintentional"* as *"a multiple-timepoint ingestion to relieve pain or other somatic symptoms with denial of suicidal intent"* and 19% of the patients with unintentional overdose used APAP for > 7 days. However, in the discussion section of the report, the authors stated that "many" of unintentional overdose patients claimed to have ingested modest amounts of APAP over weeks or months. Therefore, the ALF cases due to unintentional overdose of narcotic/APAP combination products were likely from a chronic pain patient population. The authors also commented that the chronic use of APAP or opioid/APAP combination did not seem to cause chronic liver injury.

The authors pointed out that APAP-related ALF cases were probably under-reported in the study due to the exclusion of those cases which lacked informed consent or adequate information to ensure the diagnosis. The 22 study sites represented approximately 30% of U.S. transplant capability and recorded an average of 49 APAP-related ALF cases per year over the 6-year period. They estimated that at least 250 APAP-related ALF cases per year were seen at U.S. transplant centers[41].

However, the study has the following limitations for further risk assessment of opioid/APAP combination-associated hepatotoxicity:

- More characterization of acute liver failure cases associated with opioid/APAP combinations is needed to assess any associations of opioid tolerance and physical dependence with opioid/APAP-related unintentional APAP overdose.
- Unintentional overdose should be further stratified as the "known" overdose (APAP overdose due to seeking more pain relief) and the "unknown" overdose (APAP overdose due to mistaking multiple drugs containing APAP).
- The report did not provide detailed exposure information on the opioid/APAP combination products in the ALF patients, such as duration of treatment, dosage, concurrent medications, clinical indication (acute or chronic pain), history of opioid or APAP use and concomitant medical history (particularly liver disease).
- More detailed comparisons in the APAP-related ALF between OTC and Rx products should be performed, including estimated incidences. While the incidence of APAP-related hepatotoxicity can not be calculated due to unknown actual exposure population (denominator) of acetaminophen OTC and Rx products, the population exposed to OTC products would certainly be much larger than Rx

products based on sales information. Therefore, the hepatotoxicity rate associated with opioid/APAP combination (mostly contributed by hydrocodone/APAP) would likely be higher than with the OTC products.

Spontaneous Reports of APAP-related Hepatotoxicity

A review conducted by OSE[vi] using AERS and other databases suggest that both opioid/APAP combination products and OTC APAP products are associated with APAP overdose, hepatotoxicity or death, as summarized below. However, further analyses may be needed to assess the differences in these APAP-related events between opioid/APAP and OTC APAP products and to estimate whether tolerance to and/or physical dependence on opioids and abuse/misuse of opioids play a critical role in the opioid/APAP-related events.

Overall Profile of APAP-related adverse events (AEs)

1. APAP is currently the number one marketed drug associated with acute liver failure and serious/life-threatening hepatotoxicity in the AERS database.
2. A total 25,237 serious adverse events (SAE) and non-serious AE reports for APAP were identified; 20,252 of them were domestic reports; 28% (5,581 of 20,252) had death as the outcome.
3. APAP-associated AE reports increased yearly, with 4-fold increase during the 9-year period from 1996 to 2005. The number of death reports also quadrupled from 2000 to 2005.
4. APAP was consistently the leading drug on all AE and death reports as compared to other commonly used analgesics from 2000 to 2005.
5. Completed suicide, overdose, coma and hepatic failure were among the most frequently reported AE for APAP when death was listed as an outcome.
6. There is no apparent gender difference in the number of deaths reported: 36% in females, 30% in males and 34% unknown.
7. Death reports were reported most commonly in adults aged 30-50 years.
8. APAP overdose: 6,169 reports (5,148 domestic) and 2,755 suicidal reports (2,407 domestic) in AERS (as of Aug 17, 2006). Of domestic reports, 61% (3,164) of the overdose and 86% (2,080) of suicides had a death outcome. Among overdose cases (from Epidemiologic Data section of the OSE review[vi]):
    a. 63% by OTC products
    b. 37% Rx production
    c. 3% with ≥ 2 APAP products

[vi] Chang YJ et al: OSE Safety Review: Acetaminophen, Hepatotoxicity, Overdose and Death. Feb 5, 2007

APAP-related Hepatotoxicity

1. Based on the OSE MedDRA Reaction Term Groupings "All Liver Events," APAP was listed number one among the top 10 drugs in the cumulative AERS hepatotoxicity reports: 4th in 2002, 3rd in 2003, 1st in 2004, 2nd in 2005 and 1st in 2006.
2. Based on the OSE MedDRA Reaction Term Groupings "Liver Failure", APAP was on 1st among the drugs associated with cumulative and yearly AERS liver failure reports from 2002 to 2006.
3. A total of 4,317 hepatotoxicity reports were identified in the AERS database (as of August 17, 2006), 2,862 of them were domestic reports and 52% (1,501 of 2,862) had a fatal outcome.
4. The domestic hepatotoxicity reports increased yearly since 1990 with 4-fold increase from 1995 to 2005, and the number of deaths reported increased 7-fold during the same time period.
5. The most frequently reported hepatotoxicity-associated terms with APAP were hepatic failure, increased AST and ALT, coma.
6. In an analysis of 100 fatal cases randomly selected from 1,123 APAP-related deaths identified in AERS from Jan 1 to Dec 31, 2005, 72 cases were possibly causally associated with APAP:
   a. 25% hepatic failure or necrosis (n=18), 26% cardiac or respiratory event (n=19), and 49% not reported (n=35).
   b. 67% suicide (n=48), 15% intentional misuse (n=11), 6% unintentional overdose (n=4) and 13% unknown intent (n=9).
   c. 59% on opioid/APAP combo (n=48), 39% on OTC products (n=32), 1% on other Rx combo (n=1)
      i. 65% (31 of 48) of Rx products were intentional overdose (suicide).
      ii. 21% (11 of 48) were unintentional overdose.
      iii. Hydrocodone/APAP combination products were the most frequently reported.
   d. 90% took one APAP product (n=65), 8% used two (n=8), 0% use three and 1% used four.
   e. Most of the cases did not report indication for use.

Abuse and Misuse of Opioid/APAP Combination Products

Although it is generally accepted that chronic users of opioids may develop physical dependence, a small percentage of these patients may also develop tolerance, addiction and subsequent abuse of opioid products. The development of tolerance may result in the patient increasing their dose of the combination product, inadvertently resulting in an overdose of the APAP component. In a recent survey of 335 primary care physicians in Wisconsin on the use of opioids for chronic pain, the most common concerns reported by 248 physician responders (74% of response rate) were "patients abusing the prescription" (84%), "addiction" (75%), "side effects" (68%) and "tolerance built up" (61%).[42] However, there is a paucity of good data in the literature that assess the abuse and misuse of opioid/APAP combination products in the treatment of chronic pain.

A recent study conducted in chronic non-cancer pain with one-year follow-up found that patients initially prescribed hydrocodone/APAP had the highest abuse score compared to tramadol and NSAIDs.[43] In this study, a total of 11,352 patients were enrolled and assigned to one of 3 arms: 3,145 to hydrocodone/APAP, 4,039 to non-selective NSAIDs and 4,168 to tramadol. The prescriptions (containing tramadol, NSAIDs or hydrocodone) were initially randomized to each investigator and once the subject was enrolled, the investigator could prescribe one of three drugs (became non-randomized). The abuse liability was assessed by an "abuse index" with 9 telephone interviews up to one year. The study was funded by Ortho-McNeil Pharmaceutical, the NDA holder for Ultram®, and was submitted to NDA 20-281 (Ultram®) in 2006. The adequacy of the study design, conduct and data analyses is currently under review by the Controlled Substances Staff (CSS).

Abuse liability of opioid analgesics is usually assessed in studies on chronic pain, as discussed in the systematic review articles[26-29]. These trials were not designed to evaluate abuse liability with short observation, less-well designed measures. Very limited information is available to assess tolerance and dependence. The *Opioid Guidelines in the Management of Chronic Non-Cancer Pain*[1] strongly recommends closely monitoring and documenting the abuse liability of patients who are under long-term use of opioid products for management of chronic pain.

OPTIONS

When all these factors are taken together, the overall benefit of fixed-dosed combinations of acetaminophen with opioids is questionable when compared to the risk.

The following options are some of the possible strategies that may be able to address this concern. The options are listed in the order of increasing complexity, and it must be noted that they are not mutually exclusive, since it is likely that any successful strategy will require a multi-faceted approach.

1. ***Educational outreach***

   The majority of the opioid/APAP-related acute liver failure cases reported by the Acute Liver Failure Study Group were due to unintentional APAP overdose. Some of the cases reported the use of multiple APAP-containing products, including concomitant OTC preparations. Increased awareness of APAP content in products by both health care professionals and patients is needed and such educational efforts may reduce the possibility APAP overdose. Advertisements in the traditional media (television, radio, and periodicals), as well as educational opportunities through the internet, professional conferences, or continuing medical education (CME) activities, may be useful.

   It is noted that previous outreach programs have been conducted and they have had variable success. However, there are new methods such as the FDA information

sheets which may make additional efforts worthwhile. However, it should be acknowledged that an educational approach alone is not enough. It will need to be combined with whatever other strategies are implemented and, conversely, any other strategy will have a greater chance of success if it is combined with an educational outreach component that brings attention to and explains the purpose of that particular strategy.

2. ***Labeling modification***

The package insert of all opioid/APAP combination products can be modified to include a boxed warning to highlight the fact that they, as a class, carry a risk of hepatotoxicity. This would be aimed at increasing awareness by the health care professionals (who will then, theoretically also inform patients).

3. ***Medication guide***

The creation of a medication guide may reduce the potential for APAP overdose from multiple products by increasing the likelihood that the information is being conveyed to patients.

As it has been reported that the majority of the unintentional overdoses have been due to patients taking multiple APAP-containing products, both OTC-preparations and prescription products, a medication guide could be strong counterpart to the educational outreach efforts that are ongoing with the OTC products.

4. ***Reduction of the amount of APAP in the combination***

Reformulation of the combination products so that the APAP component is only 325 mg (from the current 750 mg that can be found in certain formulations) may reduce the risk of unintentional overdose.

5. ***Uncoupling the components of the opioid/APAP combination products***

Reformulation of the combination products so that the APAP component is completely eliminated will avoid APAP-related toxicities and overdoses associated with the fixed-dose combinations. However, the 4 most commonly prescribed opioid products are APAP combination products. Whether this is due to prescriber familiarity with these products, patient preference, convenience due to their Controlled Substances Act scheduling designation, or other reasons is unclear.

It is worth noting that, per the CDER Orange Book, there are currently no approved single entity products for codeine on the U.S. market. Hydrocodone-only products available in the U.S. are formulated with a low dose of homatropine (to discourage deliberate overdosage) but are not indicated for analgesia. These products are approved for the symptomatic relief of cough, and are classified as Schedule III. Another single entity opioid product is propoxyphene, marketed in U.S. as an analgesic; it is a Schedule IV product, but it constitutes less than 5% of the prescriptions dispensed.

Although there are several approved single-entity opioid oral products (oycodone, hydromorphone, oxymorphone, fentanyl, and morphine), they may not be adequate substitutions for a patient whose pain management has been stable on the combination products for several reasons. Theses products differ from the combination products in potency, safety and tolerability profiles, and schedule designation.

There are few alternative products for physicians to prescribe under Schedule III. Codeine combinations with acetaminophen or aspirin are not as frequently prescribed as hydrocodone combination products, perhaps due to a perception of decreased efficacy and more adverse events, although there are little data to quantify these effects. Although morphine products in combination would be prescribed under Schedule III, currently there aren't any morphine combination products approved in the U.S.

Analgesics that are classified as Schedule IV, such as butorphanol, dextropropoxyphene and pentazocine, as well as unscheduled products, such as tramadol, are generally recognized to be less effective for moderate to severe pain than hydrocodone and the opioids prescribed classified as Schedule II.

Aside from the issue of needing to see their prescribers more often in order to get prescription refills which, although it may appear as a minor inconvenience, may actually be a major impediment for some patients, it is likely that that removal of these combination products will have some patients turning to other products. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally not sufficient for acute postoperative pain, however, they are considered as the first step in analgesic therapy for chronic pain, to be followed by opioids, alone or in combination, once greater analgesia is required. Hydrocodone/ibuprofen and hydrocodone/aspirin combination products are available under Schedule III, but they, like the NSAIDs, each have their own safety issues.

Therefore, reformulation of the opioid/APAP combination products to remove the acetaminophen will significantly impact the pain management options for those patients who have been, or may be, well-managed with opioid/APAP combination products.

APPENDICES

Appendix 1. List of Approved Opioid/APAP Combination Products in US

(Extracted from the CDER Orange Book on Jan 22, 2007)

Active Ingredient	Dosage Form	Strength (mg)	Proprietary Name	Indication	Dosage	ANDA	NDA
APAP, ASA, Codeine	Cap	150/180/30	*(generic name only)*			1	0
APAP, Butalbital	Cap Tab	650/50; 325/50	Bucet,, Tencon, Phrenilin, Butapap, Sedapap	Sedapap: Tension headache	1 tab q4h PRN; <6 tab/day	6	0
APAP, Butalbital, Caffeine	Cap Tab Sol	325/50/40 500/50/40 750/50/40 325/50//40 per 15 ml	Esgic-Plus Fioricet			15	0
APAP, Butalbital, Caffeine, Codeine	Cap	325/50/40/30	Phrenilin with Caffeine and Codeine; Fioricet with Codeine			5	1 (20-232)
APAP, Caffeine, Dihydrocodeine	Cap Tab	356.4/30/16 712.8/60/32	*(generic name only)*			3	0
APAP, Codeine (SC-III)	Sol Tab	120/12 per 15 ml 300-650/15-60	Codrix, Tylenol/codeine	Mild-moderately sever pain	≤ 60 mg codeine and ≤ 1 g APAP q4hr	40	0
APAP, Hydrocodone (SC-III)	Cap Tab Sol	300-750/2.5-10, 500/7.7 per 15 ml	Hydrocet, Allay, Lorcet-HD Vicodin, Zydone Anexsia, Lortab Co-Gesic, Norco	Lortab: moderate-moderately severe pain	1-2 tab q4-6h, PRN; <8 tabs per day	106	0
APAP, Oxycodone (SC-II)	Cap Tab Sol	300-650/2.5-10, 325/5 per 5 ml	Tylox, Roxilox Roxicet, OxyIR, Percocet, OxyFast, Oxycet	Percocet: moderate-moderately severe pain	1-2 tab q6h <4g APAP per day	44	0
APAP, Pentazocine (SC-IV)	Tab	650/25	Talacen	Mild-moderate pain	1 caplet q4hr as needed, ≤ 6 caplets/day	2	1 (18-415)
APAP, Propoxyphene HCl (SC-IV)	Tab	650/65	Wygesic			5	
APAP, Propoxyphene Napsylate (SC-IV)	Tab	325-650/50-100	Darvocet	Mild-moderate pain ± fever	100 mg pp/500 mg APAP q4hr as needed, ≤6 tabs/day	17	1 (17-122)
APAP, Tramadol (Un-SC)	Tab	325/37.5	Ultracet	Short-term (≤5 days) tx of acute pain		3	1 (21-123)

Approval dates for the 4 NDAs: NDA 20-232 (July 20, 1992), NDA 18-458 (Sep 23, 1982), NDA 17-122 (< Jan 1, 1982) and NDA 21-123 (Aug 19, 2001); only NDA 21-123 with factorial design study at approval.

Appendix 2. Market Share (Sales) between OTC and Rx APAP Products from Manufacturers to Retail and Non-Retail Channels of Distribution from 2001 to 2005

Laura Governale: OSE review on "OTC and Prescription Combination APAP Use," ***November 30, 2006***

- Total sales increased yearly from 2001 to 2005 for both OTC and Rx APAP products
- Proportion of Rx products increased yearly from 33% to 39%
- Proportion of OTC products decreased yearly from 67% to 61%

Market Setting	Extended Units (x1000)										% Change from 2001 to 2005
	Year 2001		Year 2002		Year 2003		Year 2004		Year 2005		
	N x1000	%	N x1000	%	N x1000	%	N x1000	%	N x1000	%	
Total OTC & Rx	24,460,290	100	25,377,600	100	27,687,155	100	26,193,116	100	28,533,925	100	16.70%
OTC Products	16,486,034	67	16,497,200	65	17,897,267	65	15,895,272	61	17,519,525	61	6.30%
Combination	8,589,645	35	8,628,253	34	9,510,219	34	8,438,389	32	9,743,544	34	13.40%
Single	7,896,389	32	7,868,947	31	8,387,048	30	7,456,883	28	7,775,981	27	-1.50%
Rx Products*	7,974,256	33	8,880,400	35	9,789,889	35	10,297,837	39	11,014,400	39	38.10%

Data are adapted from the Governale's Table 1
The original data source: IMS Health, IMS National Sales Perspectives™, Years 2001 – 2005; Source file: 0609AP01.dvr
† Retail channels include chain, independent, food-store, mail order, discount houses, and mass merchandiser pharmacies in the entire US.
‡ Non-retail channels include hospitals, long-term care facilities, clinics, home health care providers, and HMOs in the entire United States.
* Rx products are all combination products.

Appendix 3. Market Share (Dispensed Prescriptions) among Opioid/APAP Combination Products

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007 and updated by an email on January 26, 2007

- Total dispensed Rx increased yearly for hydrocodone and oxycodone and decreased yearly for propoxyphene and codeine
- The market share (Rx) from high to lower: hydrocodone, propoxyphene, codeine and oxycodone during 2000-2002; hydrocodone, oxycodone, propoxyphene and codeine during 2003-2005
- APAP combination: >98% of hydrocodone, >95% of propoxyphene, 71-77% of codeine, 66%-70% of oxycodone

Opioid Products	Year 2000				Year 2001				Year 2002			
	All Rx#	APAP Combination			All Rx#	APAP Combination			All Rx#	APAP Combination		
		Rx#	% All	% Market		Rx#	% All	% Market		Rx#	% All	% Market
Hydrocodone	76,435,066	74,985,314	98.1	52.6	81,970,478	80,491,856	98.2	54.3	87,457,644	86,080,953	98.4	55.7
Oxycodone	22,356,827	15,268,297	68.3	10.7	25,341,621	16,724,007	66.0	11.3	26,600,350	18,024,970	67.8	11.7
Propoxyphene	29,657,554	28,098,249	94.7	19.7	28,962,679	27,602,680	95.3	18.6	27,051,066	25,859,216	95.6	16.7
Codeine	29,971,097	23,210,381	77.4	16.3	29,061,536	22,126,717	76.1	14.9	26,118,971	19,833,727	75.9	12.8
Tramadol	11,463,131	Not AP			12,308,429	377,132	3.1	0.3	14,346,247	3,999,607	27.9	2.6
Others		988,947		0.7		868,581		0.6		761,803		0.5
Total		142,551,188		100.0		148,190,973		100.0		154,560,276		100.0

Opioid Products	Year 2003				Year 2004				Year 2005			
	All Rx#	APAP Combination			All Rx#	APAP Combination			All Rx#	APAP Combination		
		Rx#	% All	% Market		Rx#	% All	% Market		Rx#	% All	% Market
Hydrocodone	92,365,714	90,890,393	98.4	57.0	97,878,091	96,571,261	98.7	58.4	105,745,988	104,199,284	98.5	60.1
Oxycodone	29,157,681	19,834,591	68.0	12.4	31,229,760	21,728,512	69.6	13.2	34,317,694	24,022,444	70.0	13.8
Propoxyphene	25,943,078	24,924,404	96.1	15.6	24,956,226	23,922,635	95.9	14.5	24,021,891	23,081,684	96.1	13.3
Codeine	25,147,021	18,203,171	72.4	11.4	22,930,124	16,913,236	73.8	10.2	22,392,349	15,923,662	71.1	9.2
Tramadol	15,332,228	4,973,488	32.4	3.1	17,096,274	5,337,060	31.2	3.2	19,153,872	5,508,583	28.8	3.2
Others*		703,859		0.4		762,547		0.5		720,374		0.4
Total*		159,529,906		100.0		165,235,251		100.0		173,456,031		100.0

Data are adapted from Dr. Kendra Worthy's updated tables sent by the email of January 26, 2007.
The original data source: Verispan Vector One™: National, Years 2000-2005, data extracted on 1-26-07
* Others and Total for All Rx of opioid products (single and combination) were not available.

Appendix 4. Age Distribution of Dispensed Prescriptions of Hydrocodone/APAP Combination Products

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007

Table 5: Number of Patients, By Age, Receiving a Prescription for Hydrocodone/APAP Products Through Outpatient Retail Pharmacies from 2002-2005

Age (Years)	2002		2003		2004		2005	
	Patient Count	*Share %*	Patient Count	*Share %*	Patient Count	*Share %*	Patient Count	*Share %*
Grand Total	33,464,137	*100%*	35,518,045	*100%*	36,064,497	*100%*	38,172,533	*100%*
0-5	177,601	*0.53%*	184,318	*0.52%*	177,993	*0.49%*	179,904	*0.47%*
6-11	270,303	*0.81%*	286,958	*0.81%*	279,793	*0.78%*	290,595	*0.76%*
12-16	845,571	*2.53%*	909,110	*2.56%*	938,757	*2.60%*	975,698	*2.56%*
17-20	1,843,216	*5.51%*	1,935,259	*5.45%*	1,975,923	*5.48%*	2,070,115	*5.42%*
21-30	5,302,732	*15.85%*	5,528,563	*15.57%*	5,650,268	*15.67%*	5,793,525	*15.18%*
31-40	6,691,057	*19.99%*	6,780,268	*19.09%*	6,600,180	*18.30%*	6,654,153	*17.43%*
41-50	7,327,792	*21.90%*	7,721,156	*21.74%*	7,719,224	*21.40%*	8,074,042	*21.15%*
51-60	5,313,141	*15.88%*	5,768,137	*16.24%*	5,923,245	*16.42%*	6,546,444	*17.15%*
61-70	3,055,190	*9.13%*	3,370,551	*9.49%*	3,548,635	*9.84%*	3,943,007	*10.33%*
71-80	3,162,374	*9.45%*	3,442,020	*9.69%*	3,580,824	*9.93%*	4,033,274	*10.57%*
Unknown	69,484	*0.21%*	402,474	*1.13%*	658,565	*1.83%*	632,806	*1.66%*

Verispan: Total Patient Tracker (TPT) Data Extracted 1-2007 Source File: TPT 2006-919 Turner-Rinehardt 2006-919 hydrocodone.apap total custom age report.xls

Table 6: Percent Change, by Age, of Patients Receiving a Prescription for Hydrocodone/APAP Products Through Outpatient Retail Pharmacies

Age	2004-2005	2002-2005
Grand Total	5.85%	14.07%
0 - 5 Years	1.07%	1.30%
6 - 11 Years	3.86%	7.51%
12 - 16 Years	3.94%	15.39%
17 - 20 Years	4.77%	12.31%
21 - 30 Years	2.54%	9.26%
31 - 40 Years	0.82%	-0.55%
41 - 50 Years	4.60%	10.18%
51 - 60 Years	10.52%	23.21%
61 - 70 Years	11.11%	29.06%
71+ Years	12.64%	27.54%
Unknown Age	-3.91%	810.72%

Appendix 5. Clinical Specialties Prescribed Opioid/APAP Products

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007

Table 7: Total number of dispensed prescriptions (in thousands) for APAP containing products by prescribing specialty, Years 2002 - 2005

	2002		2003		2004		2005	
	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*	TRxs (000)	*Share %*
TOTAL MARKET	165,578	*100.0%*	169,692	*100.0%*	174,496	*100.0%*	182,287	*100.0%*
hydrocodone/APAP	86,081	*52.0%*	90,890	*53.6%*	96,571	*55.3%*	104,199	*57.2%*
GP/FM/DO	18,657	*21.7%*	20,304	*22.3%*	21,677	*22.4%*	24,305	*23.3%*
IM	10,657	*12.4%*	11,603	*12.8%*	12,380	*12.8%*	13,817	*13.3%*
DENT	11,342	*13.2%*	11,541	*12.7%*	11,894	*12.3%*	12,522	*12.0%*
ORTH SURG	8,974	*10.4%*	9,360	*10.3%*	9,427	*9.8%*	9,979	*9.6%*
UNSPEC	6,667	*7.7%*	6,282	*6.9%*	7,838	*8.1%*	7,308	*7.0%*
EM	5,770	*6.7%*	6,001	*6.6%*	6,035	*6.2%*	6,270	*6.0%*
GEN SURG	2,982	*3.5%*	3,048	*3.4%*	3,090	*3.2%*	3,184	*3.1%*
ANES	1,919	*2.2%*	2,108	*2.3%*	2,268	*2.3%*	2,501	*2.4%*
PA	971	*1.1%*	1,272	*1.4%*	1,688	*1.7%*	2,261	*2.2%*
OB/GYN	2,252	*2.6%*	2,266	*2.5%*	2,198	*2.3%*	2,222	*2.1%*
All Others	15,891	*18.5%*	17,105	*18.8%*	18,076	*18.7%*	19,830	*19.0%*
oxycodone hcl/APAP	18,025	*10.9%*	19,835	*11.7%*	21,728	*12.5%*	24,022	*13.2%*
GP/FM/DO	2,667	*14.8%*	3,097	*15.6%*	3,520	*16.2%*	4,105	*17.1%*
IM	2,061	*11.4%*	2,357	*11.9%*	2,584	*11.9%*	2,945	*12.3%*
ORTH SURG	1,826	*10.1%*	2,007	*10.1%*	2,122	*9.8%*	2,341	*9.7%*
UNSPEC	1,586	*8.8%*	1,566	*7.9%*	1,887	*8.7%*	1,754	*7.3%*
EM	1,245	*6.9%*	1,393	*7.0%*	1,523	*7.0%*	1,743	*7.3%*
DENT	1,351	*7.5%*	1,374	*6.9%*	1,405	*6.5%*	1,500	*6.2%*
OB/GYN	1,134	*6.3%*	1,167	*5.9%*	1,159	*5.3%*	1,229	*5.1%*
GEN SURG	959	*5.3%*	989	*5.0%*	998	*4.6%*	1,041	*4.3%*
AO SURG	695	*3.9%*	733	*3.7%*	765	*3.5%*	823	*3.4%*
ANES	498	*2.8%*	608	*3.1%*	707	*3.3%*	819	*3.4%*
All Others	4,004	*22.2%*	4,543	*22.9%*	5,059	*23.3%*	5,724	*23.8%*
propoxyphene nap/APAP	25,859	*15.6%*	24,924	*14.7%*	23,916	*13.7%*	23,073	*12.7%*
GP/FM/DO	7,010	*27.1%*	6,755	*27.1%*	6,359	*26.6%*	6,310	*27.3%*
IM	4,939	*19.1%*	4,830	*19.4%*	4,582	*19.2%*	4,524	*19.6%*
ORTH SURG	2,346	*9.1%*	2,291	*9.2%*	2,124	*8.9%*	2,018	*8.7%*
UNSPEC	1,985	*7.7%*	1,662	*6.7%*	1,839	*7.7%*	1,526	*6.6%*
DENT	1,319	*5.1%*	1,323	*5.3%*	1,312	*5.5%*	1,266	*5.5%*
OB/GYN	982	*3.8%*	938	*3.8%*	867	*3.6%*	783	*3.4%*
EM	844	*3.3%*	813	*3.3%*	788	*3.3%*	760	*3.3%*
GEN SURG	947	*3.7%*	885	*3.5%*	817	*3.4%*	737	*3.2%*
AO SURG	634	*2.5%*	625	*2.5%*	598	*2.5%*	563	*2.4%*
RHEUM	584	*2.3%*	581	*2.3%*	543	*2.3%*	539	*2.3%*
All Others	4,268	*16.5%*	4,221	*16.9%*	4,086	*17.1%*	4,047	*17.5%*
codeine/APAP	19,834	*12.0%*	18,203	*10.7%*	16,913	*9.7%*	15,924	*8.7%*
GP/FM/DO	3,799	*19.2%*	3,450	*19.0%*	3,127	*18.5%*	3,058	*19.2%*
DENT	3,547	*17.9%*	3,278	*18.0%*	3,047	*18.0%*	2,824	*17.7%*
IM	2,614	*13.2%*	2,381	*13.1%*	2,150	*12.7%*	2,072	*13.0%*
UNSPEC	1,946	*9.8%*	1,715	*9.4%*	1,830	*10.8%*	1,532	*9.6%*
EM	985	*5.0%*	914	*5.0%*	818	*4.8%*	773	*4.9%*
ORTH SURG	964	*4.9%*	865	*4.8%*	757	*4.5%*	693	*4.4%*
OB/GYN	897	*4.5%*	823	*4.5%*	738	*4.4%*	652	*4.1%*
ENT	667	*3.4%*	630	*3.5%*	572	*3.4%*	543	*3.4%*
PED	571	*2.9%*	560	*3.1%*	530	*3.1%*	520	*3.3%*
HOSP	413	*2.1%*	405	*2.2%*	391	*2.3%*	380	*2.4%*
All Others	3,430	*17.3%*	3,182	*17.5%*	2,952	*17.5%*	2,877	*18.1%*

Verispan, VONA, Years 2002 - 2005, Extracted November 2006; Source file: 2006-23 APAP molecule MD.qry

Table 7, continued: Total number of dispensed prescriptions (in thousands) for APAP containing products by prescribing specialty, Years 2002 - 2005

	2002		2003		2004		2005	
	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %	TRxs (000)	*Share* %
tramadol hcl/APAP	4,000	*2.4%*	4,973	*2.9%*	5,337	*3.1%*	5,509	*3.0%*
GP/FM/DO	1,154	*28.8%*	1,404	*28.2%*	1,501	*28.1%*	1,577	*28.6%*
IM	758	*18.9%*	959	*19.3%*	1,059	*19.9%*	1,179	*21.4%*
ORTH SURG	516	*12.9%*	625	*12.6%*	607	*11.4%*	578	*10.5%*
UNSPEC	396	*9.9%*	459	*9.2%*	556	*10.4%*	490	*8.9%*
RHEUM	194	*4.9%*	223	*4.5%*	220	*4.1%*	220	*4.0%*
ANES	129	*3.2%*	160	*3.2%*	172	*3.2%*	166	*3.0%*
EM	132	*3.3%*	162	*3.3%*	158	*3.0%*	154	*2.8%*
PM&R	113	*2.8%*	148	*3.0%*	146	*2.7%*	150	*2.7%*
PA	56	*1.4%*	81	*1.6%*	104	*2.0%*	122	*2.2%*
NP	43	*1.1%*	68	*1.4%*	89	*1.7%*	109	*2.0%*
All Others	510	*12.7%*	683	*13.7%*	724	*13.6%*	763	*13.9%*
APAP/caffeine/butalb	5,410	*3.3%*	5,180	*3.1%*	5,103	*2.9%*	4,738	*2.6%*
GP/FM/DO	1,872	*34.6%*	1,766	*34.1%*	1,704	*33.4%*	1,603	*33.8%*
IM	1,299	*24.0%*	1,280	*24.7%*	1,251	*24.5%*	1,173	*24.8%*
UNSPEC	494	*9.1%*	422	*8.1%*	468	*9.2%*	378	*8.0%*
NEURO	419	*7.7%*	404	*7.8%*	395	*7.7%*	376	*7.9%*
OB/GYN	244	*4.5%*	233	*4.5%*	228	*4.5%*	209	*4.4%*
NP	74	*1.4%*	87	*1.7%*	96	*1.9%*	102	*2.2%*
EM	105	*1.9%*	103	*2.0%*	104	*2.0%*	101	*2.1%*
PA	56	*1.0%*	63	*1.2%*	71	*1.4%*	74	*1.6%*
PED	74	*1.4%*	72	*1.4%*	70	*1.4%*	65	*1.4%*
PSYCH	68	*1.2%*	65	*1.3%*	63	*1.2%*	56	*1.2%*
All Others	705	*13.0%*	685	*13.2%*	653	*12.8%*	600	*12.7%*
acetaminophen	2,856	*1.7%*	2,670	*1.6%*	2,014	*1.2%*	2,202	*1.2%*
PED	776	*27.2%*	708	*26.5%*	498	*24.7%*	597	*27.1%*
UNSPEC	563	*19.7%*	684	*25.6%*	596	*29.6%*	558	*25.3%*
GP/FM/DO	690	*24.2%*	566	*21.2%*	410	*20.3%*	468	*21.3%*
IM	287	*10.1%*	246	*9.2%*	191	*9.5%*	231	*10.5%*
HOSP	99	*3.5%*	83	*3.1%*	59	*2.9%*	59	*2.7%*
EM	65	*2.3%*	64	*2.4%*	42	*2.1%*	48	*2.2%*
NP	49	*1.7%*	42	*1.6%*	30	*1.5%*	38	*1.7%*
PA	18	*0.6%*	23	*0.9%*	18	*0.9%*	28	*1.3%*
DENT	43	*1.5%*	36	*1.4%*	25	*1.3%*	27	*1.2%*
OB/GYN	29	*1.0%*	25	*0.9%*	17	*0.8%*	20	*0.9%*
All Others	237	*8.3%*	192	*7.2%*	129	*6.4%*	128	*5.8%*
All Others	3,513	*2.1%*	3,016	*1.8%*	2,912	*1.7%*	2,619	*1.4%*

Verispan, VONA, Years 2002 - 2005, Extracted November 2006; Source file: 2006-23 APAP molecule MD.qry

Appendix 6. Diagnoses Associated with Prescribing Opioid/APAP Products in Physician Office-Based Practice for Year 2002-2005

Kendra Worthy: OSE Review on "Drug Use review for acetaminophen/hydrocodone," January 23, 2007

Table 8: Top 5 Diagnoses Associated with a Mention of Opioid-APAP Combination Products in Physician Office-Based Practices, 2002-2005 (TRx: Total Rx x 1000)

	2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
TOTAL MARKET	81,310	*100.0%*	89,331	*100.0%*	91,923	*100.0%*	93,231	*100.0%*
02232 Codeine & Comb Non-Inj	48,811	*60.0%*	55,166	*61.8%*	59,887	*65.1%*	59,510	*63.8%*
hydrocodone bitartrate/apap	29,321	*60.1%*	34,579	*62.7%*	38,559	*64.4%*	38,227	*64.2%*
V670 surgery follow-up	1,556	*5.3%*	1,809	*5.2%*	2,045	*5.3%*	2,628	*6.9%*
7245 backache NOS	1,453	*5.0%*	1,983	*5.7%*	2,619	*6.8%*	2,268	*5.9%*
7242 lumbago	980	*3.3%*	1,265	*3.7%*	1,247	*3.2%*	1,397	*3.7%*
7194 pain in joint	590	*2.0%*	726	*2.1%*	854	*2.2%*	988	*2.6%*
7159 osteoarthrosis NOS	589	*2.0%*	773	*2.2%*	962	*2.5%*	862	*2.3%*
All Others	24,155	*82.4%*	28,022	*81.0%*	30,832	*80.0%*	30,084	*78.7%*
oxycodone hcl/acetaminophen	8,718	*17.9%*	9,791	*17.7%*	11,272	*18.8%*	12,471	*21.0%*
V670 surgery follow-up	564	*6.5%*	625	*6.4%*	728	*6.5%*	791	*6.3%*
7245 backache NOS	264	*3.0%*	410	*4.2%*	532	*4.7%*	790	*6.3%*
7242 lumbago	203	*2.3%*	183	*1.9%*	323	*2.9%*	578	*4.6%*
5920 calculus of kidney	247	*2.8%*	318	*3.2%*	318	*2.8%*	379	*3.0%*
7159 osteoarthrosis NOS	113	*1.3%*	164	*1.7%*	210	*1.9%*	376	*3.0%*
All Others	7,327	*84.0%*	8,092	*82.6%*	9,161	*81.3%*	9,557	*76.6%*
codeine phosphate/apap	10,705	*21.9%*	10,726	*19.4%*	10,012	*16.7%*	8,719	*14.7%*
V670 surgery follow-up	455	*4.2%*	514	*4.8%*	414	*4.1%*	307	*3.5%*
3540 carpal tunnel syndrome	160	*1.5%*	194	*1.8%*	215	*2.2%*	230	*2.6%*
8450 sprain of ankle	196	*1.8%*	143	*1.3%*	99	*1.0%*	196	*2.2%*
3829 otitis media NOS	224	*2.1%*	133	*1.2%*	162	*1.6%*	191	*2.2%*
7245 backache NOS	295	*2.8%*	354	*3.3%*	337	*3.4%*	178	*2.0%*
All Others	9,376	*87.6%*	9,386	*87.5%*	8,785	*87.7%*	7,617	*87.4%*
All Others	66	*0.1%*	71	*0.1%*	43	*0.1%*	94	*0.2%*
02120 ACETAMINOPHEN	21,578	*26.5%*	23,200	*26.0%*	21,491	*23.4%*	24,059	*25.8%*
acetaminophen	20,169	*93.5%*	22,033	*95.0%*	20,201	*94.0%*	22,742	*94.5%*
4620 acute pharyngitis	1,597	*7.9%*	1,674	*7.6%*	1,488	*7.4%*	1,901	*8.4%*
7806 pyrexia unknown origin	1,182	*5.9%*	1,346	*6.1%*	1,298	*6.4%*	1,528	*6.7%*
4659 acute URI NOS	1,510	*7.5%*	1,585	7.2%	1,403	*6.9%*	1,474	*6.5%*
3829 otitis media NOS	1,259	*6.2%*	1,357	6.2%	1,070	*5.3%*	1,253	*5.5%*
V202 routine child health exam	790	*3.9%*	1,244	5.6%	1,105	*5.5%*	1,114	*4.9%*
All Others	13,831	*68.6%*	14,827	67.3%	13,836	*68.5%*	15,471	*68.0%*
acetaminophen/caffeine/butalb	1,409	*6.5%*	1,167	5.0%	1,289	*6.0%*	1,317	*5.5%*
7840 headache	620	*44.0%*	466	39.9%	486	*37.7%*	517	*39.2%*
3469 migraine NOS	348	*24.7%*	304	26.1%	341	*26.4%*	315	*23.9%*
3078 psychalgia	247	*17.5%*	203	17.4%	274	*21.2%*	293	*22.2%*
7245 backache NOS	10	*0.7%*	24	2.1%	11	*0.9%*	22	*1.6%*
4659 acute URI NOS	--	--	15	1.2%	5	*0.4%*	16	*1.2%*
All Others	184	*13.1%*	155	13.3%	173	*13.4%*	155	*11.8%*

Table 8 (continued):

	2002		2003		2004		2005	
	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*	TRxs	*Share*
02212 PROPOXYPHENES	8,738	*10.7%*	8,069	*9.0%*	7,626	*8.3%*	7,089	*7.6%*
propoxyphene napsylate/apap	8,483	*97.1%*	7,758	*96.1%*	7,232	*94.8%*	6,700	*94.5%*
V670 surgery follow-up	414	*4.9%*	348	*4.5%*	299	*4.1%*	366	*5.5%*
7159 osteoarthrosis NOS	377	*4.4%*	338	*4.4%*	270	*3.7%*	304	*4.5%*
7245 backache NOS	525	*6.2%*	448	*5.8%*	445	*6.2%*	243	*3.6%*
7194 pain in joint	255	*3.0%*	192	*2.5%*	231	*3.2%*	239	*3.6%*
7242 lumbago	242	*2.9%*	204	*2.6%*	222	*3.1%*	167	*2.5%*
All Others	6,669	*78.6%*	6,228	*80.3%*	5,766	*79.7%*	5,380	*80.3%*
propoxyphene hcl/acetaminophen	256	*2.9%*	311	*3.9%*	375	*4.9%*	367	*5.2%*
8470 sprain of neck	9	*3.5%*	5	*1.7%*	5	*1.4%*	26	*7.0%*
7245 backache NOS	11	*4.5%*	5	*1.6%*	6	*1.7%*	23	*6.4%*
7890 abdominal pain	7	*2.8%*	--	--	9	*2.3%*	17	*4.6%*
8150 fracture metacarpal, closed	--	--	--	--	--	--	16	*4.4%*
8208 frac. neck of femur NOS, closed	--	--	5	*1.8%*	--	--	16	*4.3%*
All Others	228	*89.3%*	295	*95.0%*	355	*94.6%*	269	*73.3%*
All Others	--	--	--	--	19	*0.2%*	22	*0.3%*
02132 SYN NON-NARC NON-INJ	2,184	*2.7%*	2,889	*3.2%*	2,908	*3.2%*	2,557	*2.7%*
tramadol hcl/acetaminophen	2,184	*100.0%*	2,889	*100.0%*	2,908	*100.0%*	2,557	*100.0%*
7245 backache NOS	116	*5.3%*	218	*7.6%*	252	*8.7%*	216	*8.5%*
7159 osteoarthrosis NOS	111	*5.1%*	226	*7.8%*	144	*4.9%*	188	*7.4%*
7194 pain in joint	106	*4.9%*	96	*3.3%*	115	*4.0%*	164	*6.4%*
7242 lumbago	162	*7.4%*	159	*5.5%*	83	*2.9%*	161	*6.3%*
7840 headache	83	*3.8%*	81	*2.8%*	120	*4.1%*	86	*3.4%*
All Others	1,605	*73.5%*	2,109	*73.0%*	2,194	*75.4%*	1,742	*68.1%*
All Others	--	--	7	*0.0%*	12	*0.0%*	17	*0.0%*

Verispan, Physician Drug and Diagnosis Audit (PDDA): Years 2001 – 2005, Extracted 12/2006. Source file: PDDA 2006-919 Turner-Rinehardt 12-15-06 hydrocodone-apap diag .xls

Appendix 7. Factorial Design Studies

The following are the detailed reviews of 4 full-factorial design studies and 2 partial-factorial design studies.

7-1. Hydrocodone/APAP combination: One full-factorial design study

Beaver WT and McMillan D: Methodological considerations in the evaluation of analgesic combinations: acetaminophen (paracetamol) and hydrocodone in postpartum pain. ***Br J Clin Pharm*** 10: 215S-223S, 1980 [8]

Study design: a randomized, double-blind, placebo-controlled, 2x2 factorial design study

Subjects and Treatment: n=108 postpartum patients with either episiotomy or uterine cramp pain within 48 hours of vaginal delivery. Patients were stratified for initial pain intensity (moderate or severe) and for pain types (episiotomy or uterine cramp) and allocated to each of following treatment group (a single oral dose):

- APAP/Hydrocodone (1000/10 mg), n=21
- Hydrocodone bitartrate 10 mg, n=22
- APAP 1000 mg, n=22
- Codeine phosphate 60 mg, n=22
- Placebo, n=22

Outcome measures

- Pain intensity: 4-point categorical scale: 0=none, 1=little, 2=moderate, 3=severe
- Pain relief: 5-point scale: 0=none, 2=slight, 4=complete
- 50% pain relief: pain at least "half-gone" experienced by patients

Efficacy analysis:

- PID (change in PI from baseline)
- Total effect (AUC by totaling the hourly score for 6 hours)
- Peak effect: the first 3 hours post dosing
- Responder analysis (50% pain relief)

Results:

- No dropouts by the end of the study.
- Hydrocodone/APAP combination, hydrocodone or APAP alone were statistically superior to placebo in analgesic efficacy with a single oral dose in patients with postpartum pain during the 6-hour pain assessment (Figures 1-3, generated from the authors' Table 1).
- The combination was statically superior to hydrocodone or APAP alone in the responder analysis (50% pain relief) (Figure 3) but was not supported by results from analysis of change in pain intensity from baseline and pain relief score (Figures 1 and 2).

Comments

- Inconsistency or mutual support from different pain measures
- Limited data available for statistically analysis

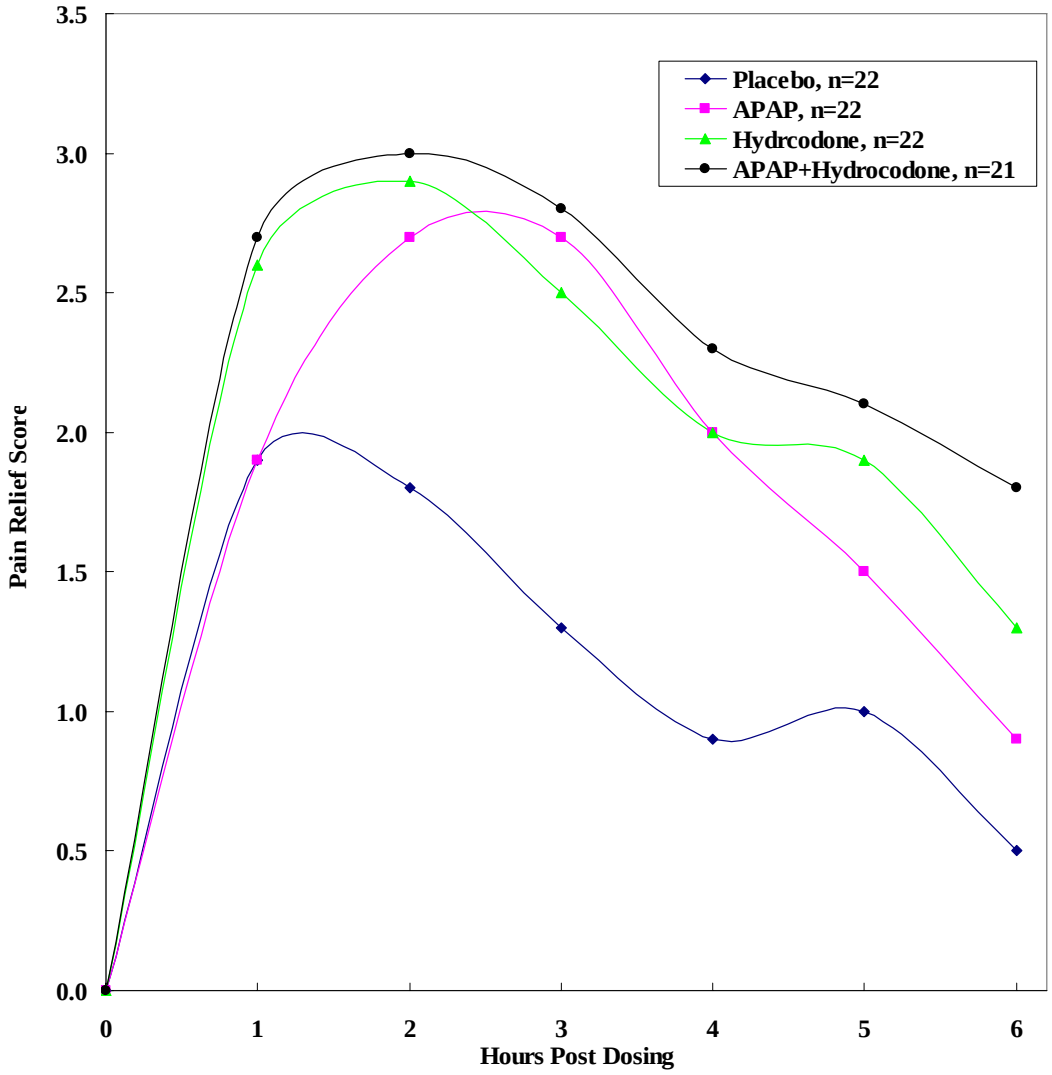

Figure 1. **Time-Course of Pain Relief Scores** in patients with postpartum pain treated with a single oral dose of hydrocodone/APAP combination (10/1000mg), hydrocodone (10 mg) alone, APAP (1000 mg) alone, or placebo. The pain relief was assessed with a 5-point categorical scale (0=none and 4=complete). Data are mean scores at each time point; the standard deviation was not reported in the article. (The figure is generated from the authors' Table 1).

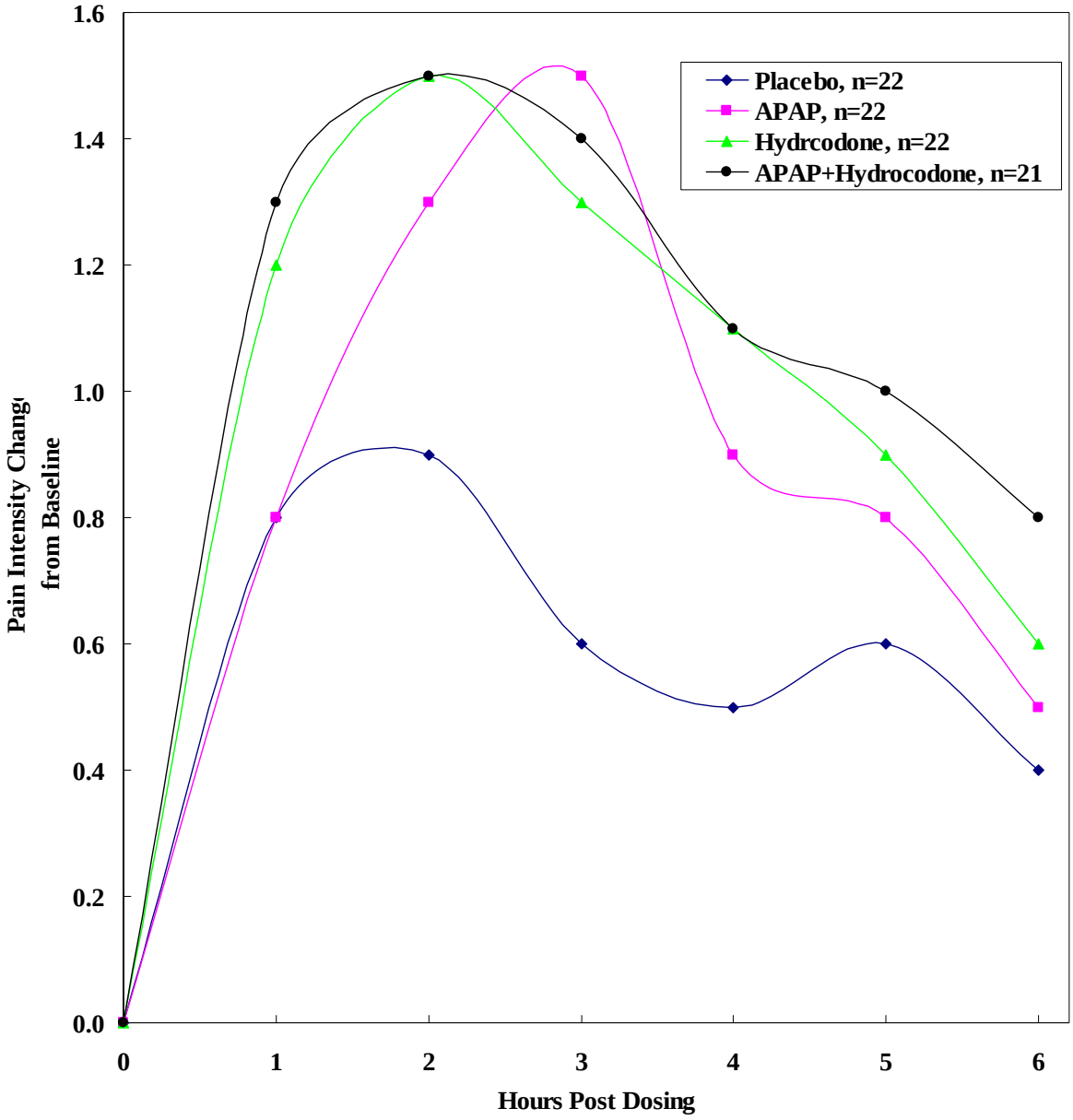

Figure 2. **Time-Course of Change in Pain Intensity from Baseline** in patients with postpartum pain treated with a single oral dose of hydrocodone/APAP combination (10/1000mg), hydrocodone (10 mg) alone, APAP (1000 mg) alone, or placebo. The pain intensity was measured with a 4-point categorical scale (0=none and 3=severe). Data are mean change scores at each time point; the standard deviation was not reported in the article. (The figure is generated from the authors' Table 1).

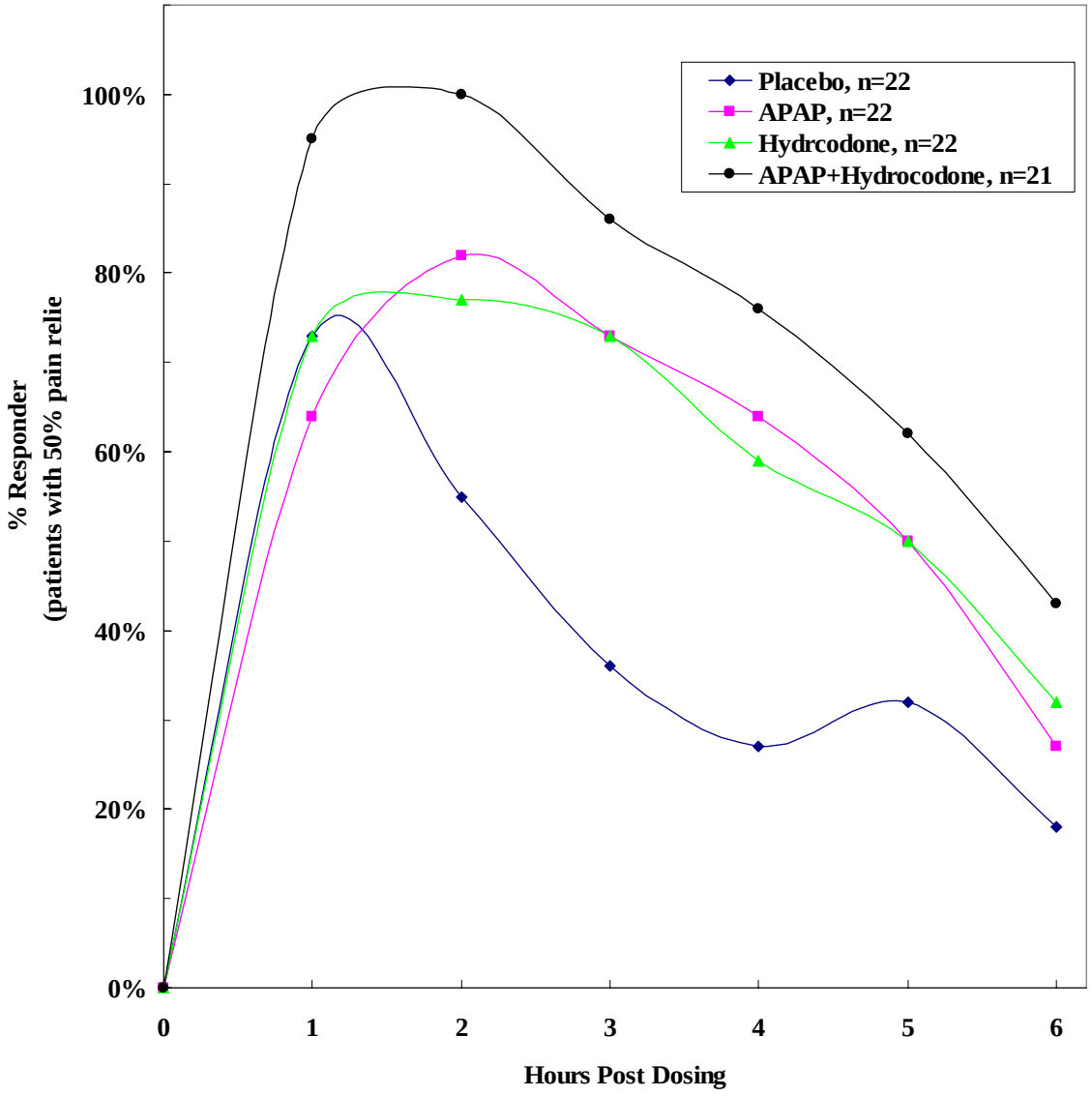

Figure 3. **Time-course of responder** in patients with postpartum pain treated with a single oral dose of hydrocodone/APAP combination (10/1000mg), hydrocodone (10 mg) alone, APAP (1000 mg) alone, or placebo. The responder was defined as patients who reported their pain at least 50% relieved. (The figure is generated from the authors' Table 1).