ANALYSIS OF POISON CONTROL CENTER DATA FOR ACETAMINOPHEN-CONTAINING PRODUCTS 1998-2000

Prepared by Julie A. Skare, PhD.
Health Care Research Center
The Procter & Gamble Company
8700 Mason-Montgomery Road
Mason, OH 45040

August 20, 2002

TABLE OF CONTENTS

ANALYSIS OF POISON CONTROL CENTER DATA FOR ACETAMINOPHEN-CONTAINING PRODUCTS* 1998-2000

1. Executive Summary

Acetaminophen (APAP) is an effective OTC analgesic/antipyretic agent with a long history of widespread use in over-the-counter medications including both single ingredient products for pain relief/fever reduction and combination multiple symptom relief cough and cold products. When used according to label directions, APAP has an outstanding safety profile. Under circumstances of overdose of APAP, hepatotoxicity may occur due to the formation of an excess of a highly reactive metabolite by hepatic P450 enzymes. In order to respond to the FDA's request for information to better understand the root causes of incidents involving hepatotoxic outcomes, an analysis of poison control center data for all APAP-containing cough and cold products and APAP-containing analgesics has been completed. The Toxic Exposure Surveillance System (TESS) established by the American Association of Poison Control Centers (AAPCC) is a well recognized source of post-marketing surveillance data that has contributed to decisions related to the safety of many types of products including drugs. Poison control centers participating in TESS serve approximately 96% of the U.S. population.

For this analysis AAPCC TESS data for three classes of products were purchased for the years 1998-2000. These three data sets include:

A) All APAP-containing multisymptom relief cough and cold products (N=60612 cases)

B) All APAP-containing analgesic products (N=316371 cases)

C) All multisymptom relief cough and cold products that do not contain an analgesic (N=206428 cases)

The AAPCC TESS data were analyzed to determine medical outcome as a function of reason for exposure for all cases in each of the three data sets. For each of the three data sets, the profile of all reported clinical effects was examined as a function of reason for exposure. Specifically focusing on only those cases involving hepatic effects, each of the three data sets was then analyzed to determine the number of cases involving hepatic effects as a function of the reason for exposure and as a function of the severity of the medical outcome. Cases involving hepatic effects were identified by searching for cases in which the following clinical effects were reported: $100<AST/ALT\leq 1000$, AST/ALT>1000, bilirubin increased, disseminated intravascular coagulation, PT prolonged, other coagulopathy, or other liver function test (LFT) abnormality. Only those cases in which one or more of these clinical effects was judged by the poison control center to be related to or of unknown relationship to the exposure were counted. Cases in which the hepatic clinical effect(s) was judged by the poison control center to be not related to the exposure were excluded.

*The content of this report does not necessarily reflect the opinions or conclusions of the American Association of Poison Control Centers.

For the two data sets involving APAP-containing products, information on the type of APAP-containing product used and whether or not more than one APAP-containing product was used was also analyzed as a function of the reason for exposure for all hepatic effects cases excluding suspected suicide attempts.

The following observations can be made from the analysis of the data presented in this report.

- For all three data sets, the majority of cases handled by the poison control centers involved no clinical effects (25-29%), minor effects (~15%) (typical symptoms were drowsiness, nausea, vomiting), or received no or minimal follow-up because the quantities ingested were expected to result in no or minimal clinical effects (38-49%).

- For the APAP-containing cough and cold products data set, less than 0.3% of the total number of cases involved hepatic effects, and the majority of these (66%) were suspected suicide attempts. For the APAP-containing analgesics data set, 2% of the total number of cases involved hepatic effects and the majority of these (70%) were suspected suicide attempts. An extremely small fraction (0.006%) of cases involving cough and cold medications without analgesic involved hepatic effects, and approximately half of these were suspected suicide attempts.

- Excluding suspected suicide attempts, hepatotoxicity cases with serious medical outcomes (i.e., major effects and deaths) accounted for 35% (19/54) of the total number of hepatotoxicity cases for the APAP-containing cough and cold products data set and for 41% (768/1877) of the total number of hepatotoxicity cases for the APAP-containing analgesics data set.

- Hepatotoxicity cases were divided approximately evenly between unintentional reasons for exposure and intentional reasons for exposure, excluding suspected suicide attempts. This was true for both the APAP-containing analgesics and the APAP-containing cough and cold products.

- An in depth analysis of products involved in hepatotoxicity cases for the year 2000 revealed the following profile:

Product(s) Used	**Number of Cases (N=698)**	**% of Cases**
One Single Ingredient OTC APAP Analgesic	455	65%
One Combination Product (Rx or OTC) • Rx Analgesic Combo • OTC Combo (Not cough/cold) • OTC Combo (Cough/cold)	178 • 111 • 54 • 13	26% • 16% • 8% • 2%
Two APAP Products	59	8%
Three or more APAP Products	6	<1%

From these data it is clear that the majority of hepatotoxicity cases involved the use of one APAP-containing analgesic product, most frequently a single ingredient OTC analgesic. APAP-containing cough and cold medications were not a significant contributor to the total number of poison control center reports of APAP-associated hepatotoxicity.

- Concomitant use of more than one APAP-containing product was not a major root cause of incidents involving hepatotoxicity. Less than 10% of hepatotoxicity cases involved the use of more than one APAP-containing product (see the table above). Among those cases involving more than one product, the concomitant use of a single ingredient OTC analgesic plus an Rx combination analgesic was the most frequently reported (27 cases or ~4% of hepatotoxicity cases). The use of an OTC APAP-containing cough and cold product plus one or more other APAP-containing product(s) was reported in 8 cases (~1% of hepatotoxicity cases).

- During the three year period evaluated there were no reported cases involving hepatic effects with the use of an APAP-containing cough and cold medication as recommended. Such cases would have been classified as adverse drug reactions according to AAPCC TESS definitions, and none of these were reported. There were a small number of adverse drug reactions with hepatic effects reported for the APAP-containing analgesic products (36 cases representing 0.01% of total cases). However, insufficient information is available on these cases to conduct a thorough assessment of causality ruling out other possible causes or to reliably document whether or not the amount of APAP take was truly within the recommended therapeutic dose.

Taken as a whole, these data indicate that cases of hepatotoxicity associated with APAP-containing products result from the intentional or unintentional incorrect use of these products. Cases involving hepatic effects with recommended therapeutic use are very rare and impossible to confirm given the limitations inherent in data collection. Intentional or unintentional incorrect use of these products can be addressed by labeling changes and by public education programs that inform consumers about products containing APAP and the potential for serious consequences associated with overdosing.

2. Background

The FDA has sought information from the OTC health care industry on the root causes for cases of hepatotoxicity associated with the use of acetaminophen (APAP)-containing OTC products so that informed decisions can be made regarding possible means for decreasing the occurrence of these incidents. Possible scenarios the FDA has suggested as root causes for these cases are 1) the consumer ingested more than the recommended dose of a single APAP-containing product, 2) the consumer used an OTC combination product containing APAP along with an OTC single ingredient APAP analgesic product either unintentionally (i.e., not knowing that they both contain APAP) or intentionally (but without understanding the possible adverse effects associated with overdose), 3) the consumer used an Rx product containing APAP along with an OTC single ingredient APAP analgesic product either unintentionally or intentionally, or 4) the consumer developed liver toxicity even though he/she followed the label directions for use. In response to the FDA's request for information, poison control center data for APAP-containing cough and cold medications and APAP-containing analgesics have been purchased from the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS), and an analysis of cases involving hepatic effects has been completed. The AAPCC TESS data provide an additional source of post-marketing adverse event data that can be evaluated in conjunction with the FDA's AERS database to obtain a more complete picture of post-marketing adverse event reports of hepatotoxicity associated with APAP.

3. Methods

AAPCC TESS data for three classes of products were purchased for the years 1998-2000. These three data sets include:

D) All APAP-containing multisymptom relief cough and cold products

E) All APAP-containing analgesic products

F) All multisymptom relief cough and cold products that do not contain an analgesic

The subcategories of products that are included in each of these three data sets are shown in Figures 1 – 3 below. These subcategories reflect the classification system used by AAPCC TESS. This classification system was created several years ago, and there are not necessarily currently marketed products that fall into each of the subcategories listed in Figures 1 – 3.

OTC APAP-containing cough and cold combination products (Figure 1) typically contain a decongestant plus an antihistamine, and they may also contain an antitussive (e.g., dextromethorphan). The AAPCC TESS category of APAP-containing analgesics (Figure 2) includes OTC single ingredient APAP analgesic products (either an adult formulation, a pediatric formulation, or unknown whether adult or pediatric), OTC APAP combination products containing aspirin, Rx combination products containing an opioid, and other combination products such as OTC analgesic/sleep aid combination products containing APAP plus diphenhydramine. Cough and cold products without an analgesic (Figure 3) typically contain the same types of active ingredients as the APAP-containing cough and cold combinations except that they do not contain APAP, aspirin, or any other analgesic.

Figure 1
AAPCC TESS Classifications for APAP-Containing Cough and Cold Products

APAP/ASA with decongestant/antihistamine, with phenylpropanolamine, and:
- Dextromethorphan
- Other opioid
- Without opioid

APAP/ASA with decongestant /antihistamine, without phenylpropanolamine, and:
- Dextromethorphan
- Other opioid
- Without opioid

APAP with decongestant/antihistamine, with phenylpropanolamine, and:
- Codeine
- Dextromethorphan
- Other opioid
- Without opioid

APAP with decongestant/antihistamine, without phenylpropanolamine
- Codeine
- Dextromethorphan
- Other opioid
- Without opioid

APAP/dextromethorphan

Figure 2
AAPCC TESS Classifications for Acetaminophen-Containing Analgesics

Acetaminophen only
- Adult formulation
- Pediatric formulation
- Unknown formulation

Acetaminophen in combination with:
- Aspirin with other ingredient
- Aspirin without other ingredient
- Codeine
- Hydrocodone
- Oxycodone
- Propoxyphene
- Other opioid
- Other drug: adult formulation
- Other drug: pediatric formulation

Figure 3
AAPCC TESS Classifications for Cough and Cold Products Without Analgesic

Antihistamine/decongestant, with phenylpropanolamine:
- Codeine
- Dextromethorphan
- Other opiod
- Without opioid

Antihistamine/decongestant, without phenylpropanolamine:
- Codeine
- Dextromethorphan
- Other opioid
- Without opioid

Other dextromethorphan

Other phenylpropanolamine

Other

The AAPCC TESS data were analyzed to determine medical outcome as a function of reason for exposure for all cases in each of the three data sets. Within each data set, medical outcome as a function of reason for exposure was also evaluated for three different age groups: 1) < 6 years of age, 2) 6-12 years of age, and 3) >12 years of age. The AAPCC TESS definitions for reasons for exposure and medical outcome are provided below (Figures 4 and 5).

For each of the three data sets, the profile of all reported clinical effects was examined as a function of reason for exposure. Specifically focusing on hepatoxicity, each of the three data sets was also analyzed to determine the number of cases involving hepatic effects as a function of the reason for exposure and as a function of the severity of the medical outcome. The data were analyzed by age group as described above. Cases involving hepatic effects were identified by searching for cases in which the following clinical effects were reported: $100<AST/ALT\leq1000$, AST/ALT>1000, bilirubin increased, disseminated intravascular coagulation, PT prolonged, other coagulopathy, or other liver function test (LFT) abnormality. Only those cases in which one or more of these clinical effects was judged by the poison control center to be related to or of unknown relationship to the exposure were counted. Cases in which the hepatic clinical effect(s) was judged by the poison control center to be not related to the exposure were excluded.

For the two data sets involving APAP-containing products, information on the type of APAP-containing product used and whether or not more than one APAP-containing product was used was also analyzed as a function of the reason for exposure for all hepatic effects cases excluding suspected suicide attempts. For the APAP-containing cough and cold products, the analysis of products used covered all three years (1998-2000). The year 2000 was the first year that the AAPCC TESS system captured data on the use of more than two

substances per case. Nevertheless, all three years were included in this analysis because the total number of hepatic effects cases was relatively small for the APAP-containing cough and cold products data set. For the larger number of cases involving the APAP-containing analgesic products, the analysis of products used was limited to the year 2000.

Figure 4
AAPCC TESS Definitions
Medical Outcome

No Effect: The patient developed no signs or symptoms as a result of the exposure

Minor Effect: The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly.

Moderate Effect: The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more of a systemic nature than minor symptoms. Symptoms were not life-threatening, and the patient has no residual disability. Usually some form of treatment is indicated.

Major Effect: The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement

Death: Only those deaths which are probably or undoubtedly related to the exposure are coded here.

No Follow-Up, Nontoxic Exposure: Follow-up calls were limited because the substance implicated was nontoxic or the amount was insignificant

No Follow-Up, Minimal Effects Possible: Follow-up calls were limited because the exposure was likely to result in only minimal toxicity.

Unable to Follow, Potentially toxic: The exposure was significant and may have resulted in a moderate, major or fatal outcome, but the patient could not be followed

Unrelated Effect: The exposure was probably not responsible for the effect.

Figure 5
AAPCC TESS Definitions
Reasons for Exposure

Unintentional General: All unintentional exposures not specifically defined below. Most unintentional exposures in children are captured here.

Therapeutic Error: An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only exposures to medications or products substituted for medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are known to interact are also included.

Unintentional Misuse: Unintentional improper or incorrect use of a nonpharmaceutical substance. (In the data sets included in this analysis, cases coded as Unintentional Misuse most likely represent Therapeutic Error cases that have been misclassified since the substances involved are pharmaceutical substances.)

Unintentional Unknown: An exposure determined to be unintentional but the exact reason is unknown

Suspected Suicidal: Inappropriate use of a substance for reasons which are suspected to be self destructive or manipulative.

Intentional Misuse: Intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.

Intentional Abuse: Intentional improper or incorrect use of a substance to achieve a euphoric or psychotropic effect. All recreational use of substances for any effect is included.

Adverse Reaction: An adverse event occurring with normal, prescribed, labeled or recommended use of the product, as opposed to overdose, misuse, or abuse.

Other: Several categories from the AAPCC TESS definitions were combined together into one "Other" category. These include: Environmental, Occupational, Bite/Sting, Food Poisoning, Contaminant/Tampering, Malicious, Adverse Reaction to Food

4. Results

For all of the data discussed below, summary tables and figures are provided in the text and more detailed tables are included in Appendices A - C.

4.1 APAP-Containing Cough and Cold Medications

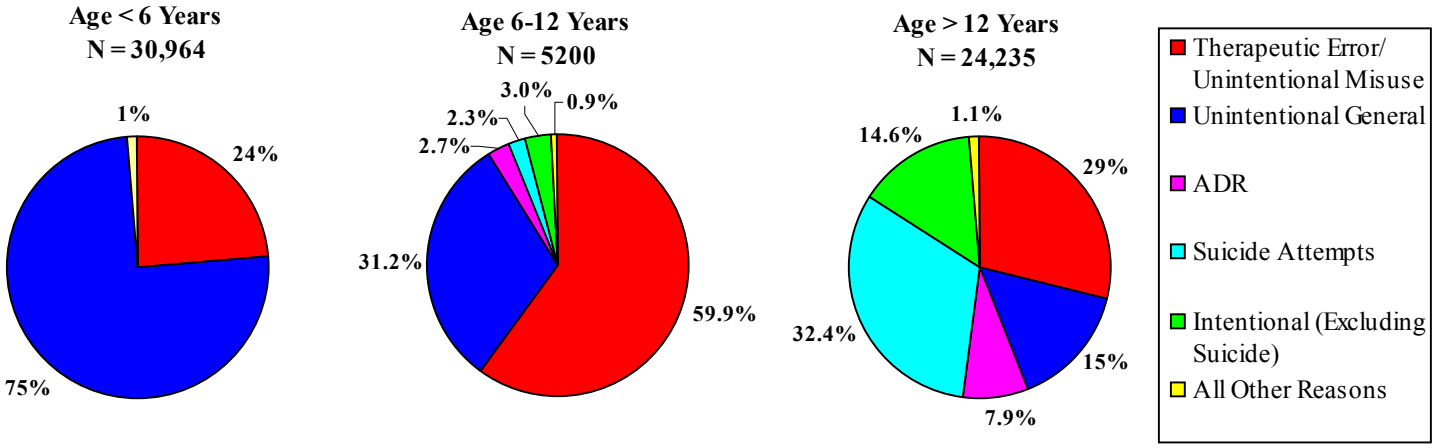
4.1.1 Medical Outcome and Reason for Exposure – All Cases (Tables A1-A4, Appendix A)

There were a total of ~20,000 reports per year for products included in this data set resulting in a total of over 60,000 cases during the three year period. The majority of cases involved

no clinical effects (~25%), minor effects (~16%), or received no or minimal follow-up because the quantities ingested were expected to result in no or minimal clinical effects (~47%). Serious medical outcomes (i.e., major effects and deaths) accounted for ~0.3% of cases, and the majority of these (~84%) were associated with intentional exposures, predominantly suicides/suicide attempts (see Table A1, Appendix A).

The predominant reason for exposure for all cases involving APAP-containing cough and cold products reported to poison control centers during 1998-2000 varied among the three different age groups evaluated (see Figure 6 below and Tables A2-A4, Appendix A). Among children <6 years of age, unintentional general cases (i.e., accidental ingestions) predominated (75% of cases), and therapeutic errors/unintentional misuse accounted for most of the remaining cases (24%). Among children 6–12 years of age, therapeutic errors/unintentional misuse were the most frequently reported reason (~60%), and unintentional general cases were the second most frequently reported reason (~31%). Among those age >12 years, suspected suicide attempts (~32%) and therapeutic errors/unintentional misuse (~29%) were the most frequently reported reasons.

Figure 6
APAP-Containing Cough and Cold Medications
Reason for Exposure – All Cases



4.1.2 Clinical Effects – All Cases (Table A5, Appendix A)

The total number of clinical effects reported by body system was evaluated by broad category of reason for exposure (i.e., unintentional, intentional, adverse drug reaction, other, unknown) and these data are summarized in Table 1 below. Only clinical effects judged by the poison control center to be related or of unknown relationship to the exposure were counted. Clinical effects judged by the poison control center to be not related to the exposure were excluded. The most frequently reported clinical effects (see Table A5, Appendix A) were drowsiness/lethargy (15.5% of cases), tachycardia (4.1%), vomiting (3.3%), agitation/irritability (3.2%), dizziness/vertigo (2.8%), and nausea (2.2%). One or more hepatic effects were observed in 0.27% of cases (162/60612) (see Table A6, Appendix A).

Table 1
APAP-Containing Cough and Cold Medications
Summary of Clinical Effects by Reason for Exposure*
1998-2000 – All Cases, All Ages

	Number of Clinical Effects					
Body System	**Unintentional (N=46181 Cases)**	**Intentional** (N=11853 Cases)**	**Adverse Drug Reaction (N=2261 Cases)**	**Other (N=130 Cases)**	**Unknown (N=187 Cases)**	**Total (N=60612 Cases)**
Cardiovascular	579	2613	234	6	33	3465
Dermal	178	120	506	0	4	808
Gastrointestinal	1435	2313	292	8	21	4069
Hepatic/Hematological	48	224	1***	0	0	273
Neurological	8190	6412	1109	21	111	15843
Ocular	289	529	75	8	4	905
Renal	14	51	2	0	0	67
Respiratory	94	167	69	2	8	340
Miscellaneous	920	954	445	4	39	2362
Total Number of Clinical Effects	**11747**	**13383**	**2733**	**49**	**220**	**28132**

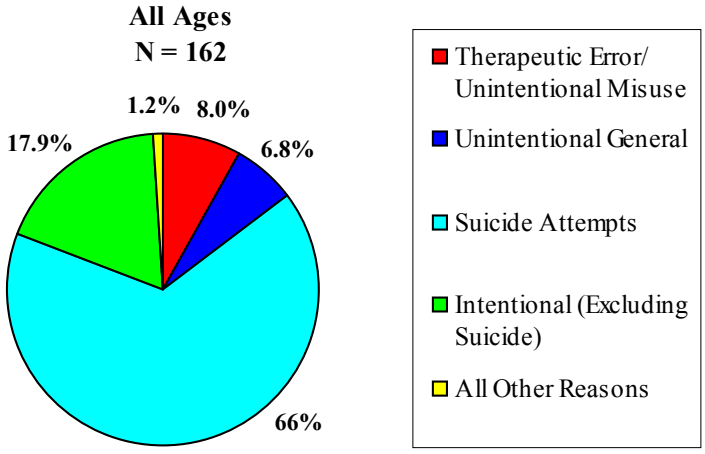
*More than one clinical effect may be reported per case
**Includes suspected suicide attempts
***Reported clinical effect was hemolysis

4.1.3 Medical Outcome and Reason for Exposure – Hepatic Effect Cases (Tables A6-A7a-h, Appendix A)

Cases involving hepatic effects were tabulated according to medical outcome and reason for exposure. The majority of these cases (107/162, ~66%) involved suspected suicide attempts (see Figure 7 below and Table A6, Appendix A). Other intentional reasons for exposure (i.e., intentional abuse, intentional misuse) accounted for ~18% of cases. Therapeutic errors/unintentional misuse accounted for 8% of cases, and unintentional general cases represented 6.8% of cases. There were no cases involving hepatic effects when label directions were followed (i.e., adverse drug reactions). Because there were only two cases

involving children <12 years of age, Figure 7 includes all ages but does not display reason for exposure by age group.

Figure 7
APAP-Containing Cough and Cold Medications
Reason for Exposure – Hepatic Effect Cases



For the APAP-containing cough and cold medications, there were 25 cases with hepatic effects that involved unintentional exposures (i.e., taking too much by mistake) and 29 cases with hepatic effects (excluding suicide attempts) that involved intentional exposures (i.e., taking too much on purpose) (see Tables 2a and 2b below). Among these 54 cases, there was 1 death (a therapeutic error in a 78 year old female) and 18 cases with major medical outcomes. Among these 19 serious cases, 9 involved unintentional reasons for exposure and 10 involved intentional reasons for exposure. Although the total number of hepatic effects cases was comparable for unintentional and intentional reasons for exposure (25 vs. 29), the percentage of cases with hepatic effects (0.05% vs. 0.8%) and the percentage of cases with serious medical outcomes involving hepatic effects (deaths plus major effect medical outcomes) (0.02% vs. 0.3%) was much lower for unintentional reasons for exposure in comparison to intentional reasons for exposure. Two of the cases classified as unintentional general cases involved two year olds, and most likely involved accidental ingestions by unattended children. Neither of these cases involved a serious medical outcome although one of them was not followed. There were no other hepatic effect cases involving children <12 years of age. A listing of the 54 cases involving hepatic effects that provides information on age, gender, medical outcome, reason for exposure, reported clinical effects, and substances used is found in Tables A7a-h, Appendix A.

Table 2a
APAP-Containing Cough and Cold Medications
Medical Outcome for Cases Involving Hepatic Effects
Unintentional Exposures

Medical Outcome	Unintentional General	Therapeutic Error	Unintentional Misuse	Unintentional Unknown	Total (% of Total)
Minor Effect	2*	0	0	0	2 (0.004)
Moderate Effect	5	2	0	0	7 (0.02)
Major Effect	1	4	2	1	8 (0.02)
Death	0	1	0	0	1 (0.002)
No F/U-Minimally Toxic	0	0	0	0	0
No F/U-Potentially Toxic	3*	2	2	0	7 (0.02)
Total Cases with Hepatic Effects	11	9	4	1	25 (0.05)
TOTAL CASES	28514	16070	1521	76	46181

*Includes one case involving a two year old child in each of these categories.

Table 2b
APAP-Containing Cough and Cold Medications
Medical Outcome for Cases Involving Hepatic Effects
Intentional Exposures (Excluding Suicides)

Medical Outcome	Intentional Misuse	Intentional Abuse	Intentional Unknown	Total (% of Total)
Minor Effect	1	1	1	3 (0.08)
Moderate Effect	5	8	1	14 (0.4)
Major Effect	5	5	0	10 (0.3)
Death	0	0	0	0
No F/U-Minimally Toxic	0	0	0	0
No F/U-Potentially Toxic	2	0	0	2(0.05)
Total Cases with Hepatic Effects	13	14	2	29 (0.8)
TOTAL CASES	1888	1402	478	3768

4.1.4 Demographics of Cases Involving Hepatic Effects

Age and gender distribution were examined for hepatic effect cases involving unintentional or intentional (excluding suicides) reasons for exposure (see Table 3 below). There appeared to be a larger proportion of males in cases involving intentional reasons for exposure, although the total number of cases was too small to draw firm conclusions.

Table 3
APAP-Containing Cough/Cold Medications
Demographics for Cases Involving Hepatic Effects
1998-2000

Reason for Exposure	N	Mean Age ± SD (Range)	Gender
Unintentional General	11	29 ± 16.2 (2-48)	6M/5F
Therapeutic Error	9	56 ± 17.1 (21-78)	3M/6F
Unintentional Misuse	4	42 ± 3.7 (37-46)	2M/2F
Unintentional Unknown	1	19	F
Total Unintentional	**25**	**40 ± 16.1 (2-78)**	**11M/14F**
Intentional Misuse	13	32 ± 10.3 (17-50)	11M/2F
Intentional Abuse	14	27 ± 16.4 (13-70)	10M/4F
Intentional Unknown	2	16 ± 0	1M/1F
Total Intentional*	**29**	**27 ± 8.2 (13-70)**	**22M/7F**

*Excludes suspected suicide attempts

4.1.5 Products Involved in Hepatic Effect Cases – Cough and Cold Medications (Tables A8-A10, Appendix A)

Hepatic effects cases involved only one APAP-containing cough and cold product and no other APAP-containing product in 18/25 cases and 21/29 cases for the unintentional and intentional reasons for exposure, respectively (Table 4 and Tables A8 and A9, Appendix A). When there was another APAP product involved, it was most often a single ingredient OTC analgesic (9 cases). In two of the cases involving intentional reasons for exposure, three APAP-containing products were used. The cases included in the data set for APAP-containing cough and cold medications that also involved use of an APAP-containing analgesic are also found in the data set for the APAP-containing analgesics discussed in the Section 4.2 below.

The number of APAP-containing products used was also evaluated by medical outcome (Table A10, Appendix A) in order to determine whether or not there appeared to be a trend for multiple product use to result in more significant medical outcomes involving hepatic effects. However, the number of hepatic effects cases in the cough and cold medications data set was too small to draw any conclusions regarding this question.

Table 4
Products Used in Hepatic Effect Cases
APAP-Containing Cough and Cold Medications Data Set
1998-2000

	No. of Cases	No. of Cases				No. of Cases	
Reason for Exposure	**One APAP-Containing Cough/Cold Product**	**Two APAP Products**				**Three APAP Products**	**Total**
		Cough/Cold Product + OTC Analgesic	Cough/Cold Product +Rx Analgesic	Cough/Cold Product + Analgesic/Sleep Aid	Two Cough/Cold Products	Any Three Products	
Unintentional General	9	1	1	0	0	0	11
Therapeutic Error	6	1	1	0	1	0	9
Unintentional Misuse	3	1	0	0	0	0	4
Unintentional Unknown	0	1	0	0	0	0	1
Subtotal Unintentional	**18**	**4**	**2**	**0**	**1**	**0**	**25**
Intentional Misuse	8	4	0	0	0	1	13
Intentional Abuse	11	1	0	1	0	1	14
Intentional Unknown	2	0	0	0	0	0	2
Subtotal Intentional*	**21**	**5**	**0**	**1**	**0**	**2**	**29**
Total	**39**	**9**	**2**	**1**	**1**	**2**	**54**

*Excludes suspected suicide attempts

4.2 APAP-Containing Analgesics

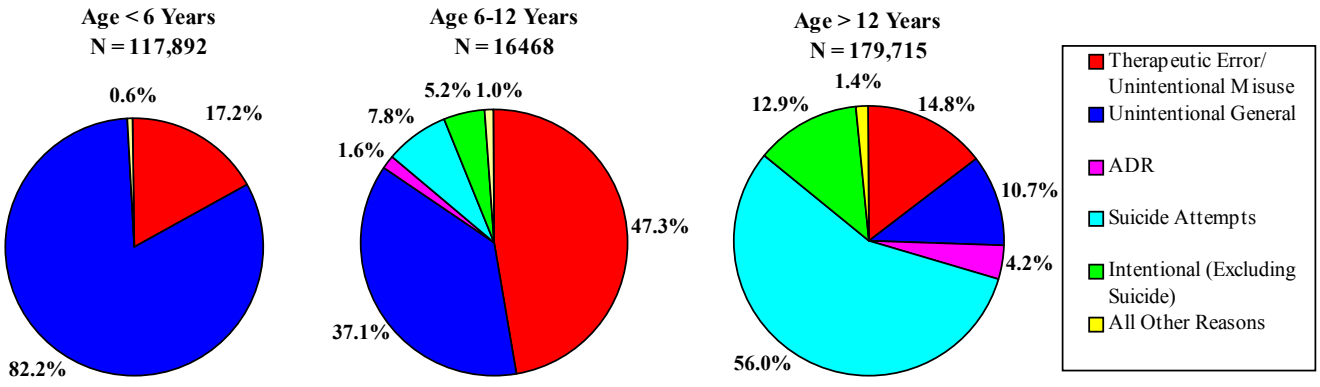
4.2.1 Medical Outcome and Reason for Exposure – All Cases (Tables B1-B4, Appendix B)

There were a total of ~100,000 reports per year for products included in this data set resulting in a total of over 300,000 cases during the three year period. Similar to the APAP-containing cough and cold medications, the majority of cases involved no clinical effects (~27%), minor effects (~15%), or received no or minimal follow-up because the quantities ingested were expected to result in no or minimal clinical effects (~38%). Serious medical outcomes (major effects and deaths) accounted for ~1.8% of cases, which represents a notably higher percentage than the APAP-containing cough and cold products (~0.3%). The majority of

these serious outcomes (~87%) were associated with intentional exposures, predominantly suicides/suicide attempts (see Table B1, Appendix B).

As with the APAP-containing cough and cold medications, the predominant reason for exposure for all cases reported to poison control centers varied among different age groups (see Figure 8 below and Tables B2-B4, Appendix B). Among children <6 years of age, unintentional general cases (i.e., accidental ingestions) predominated (~82% of cases) and therapeutic errors/unintentional misuse accounted for most of the remaining cases (~17%). Among children 6-12 years of age, therapeutic errors/unintentional misuse were the most frequently reported reason (~47%), and unintentional general cases were the second most frequently reported reason (~37%). Among those age >12 years, suspected suicide attempts were the most frequently reported and accounted for a higher percentage of total cases (~56%) than for the APAP-containing cough and cold medications. Therapeutic errors/unintentional misuse (~15%) were the second most frequently reported reason.

Figure 8
APAP-Containing Analgesics
Reason for Exposure – All Cases



4.2.2 Clinical Effects – All Cases (Table B5, Appendix B)

The total number of clinical effects reported by body system was evaluated by broad category of reason for exposure (i.e., unintentional, intentional, adverse drug reaction, other, unknown) and these data are summarized in Table 5 below. Only clinical effects judged by the poison control center to be related or of unknown relationship to the exposure were counted. Clinical effects judged by the poison control center to be not related to the exposure were excluded. The most frequently reported clinical effects were drowsiness/lethargy (13.7% of cases), vomiting (8.3%), nausea (5.1%), tachycardia (3.4%), abdominal pain (2.2%), and agitation/irritability (2.0%) (see Table B5, Appendix B). Although these were generally similar to the most frequently reported clinical effects for the APAP-containing cough and cold medications (see Section 4.1.2), one notable difference was that the frequency of hepatic effects was greater for the APAP-containing analgesics. One or more hepatic effect(s) were observed in 2.0% (6360/316371) of cases (see Table B6, Appendix B) compared to 0.27% (162/60612) of cases for the APAP-containing cough and cold products (see Section 4.1.2).

Table 5
APAP-Containing Analgesics
Summary of Clinical Effects by Reason for Exposure*
1998-2000 - All Ages

	Number of Clinical Effects					
Body System	**Unintentional (N=178206 Cases)**	**Intentional** (N=127772 Cases)**	**Adverse Drug Reaction (N=8289 Cases)**	**Other (N=569 Cases)**	**Unknown (N=1535 Cases)**	**Total (N=316371 Cases)**
Cardiovascular	1530	16013	401	3	223	18170
Dermal	786	976	2077	4	22	3865
Gastrointestinal	10776	37454	3113	58	276	51677
Hepatic/Hematological	1587	10298	86	7	282	12260
Neurological	14727	58426	3368	41	890	77452
Ocular	506	2215	109	3	52	2285
Renal	156	1174	29	2	61	1422
Respiratory	566	3755	350	1	123	4795
Miscellaneous	3143	11401	1568	13	280	16405
Total Number of Clinical Effects	**33777**	**141712**	**11101**	**132**	**2209**	**188931**

*More than one clinical effect may be reported per case
**Includes suspected suicide attempts

4.2.3 Medical Outcome and Reason for Exposure – Hepatic Effects Cases (Tables B6-B11, Appendix B)

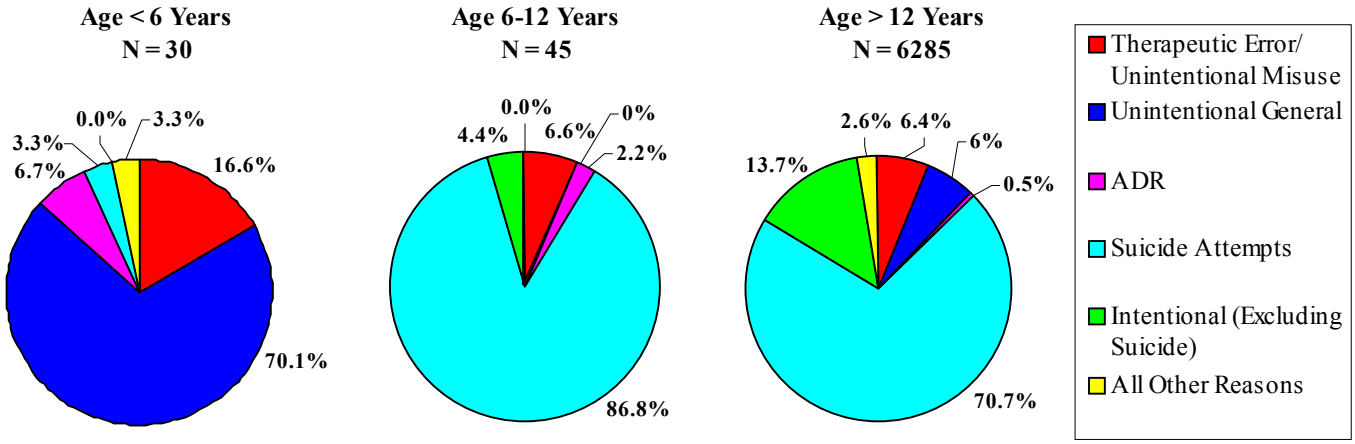
Cases with hepatic effects were tabulated according to medical outcome and reason for exposure. The vast majority of cases with hepatic effects (6285/6360, ~99%) involved subjects >12 years of age (see Tables B6-B9, Appendix B). There were 30 cases involving children < 6 years of age and 45 cases involving children 6-12 years of age.

Reasons for exposure among cases with hepatic effects varied for the three different age groups evaluated (see Figure 9 below and Tables B7-B9, Appendix B). Among children <6 years of age, unintentional general exposures (i.e., accidental ingestions) accounted for ~72% of hepatic effect cases (21 cases). Therapeutic errors/unintentional misuse accounted for ~17% of cases (5 cases). There were 2 cases classified as adverse drug reactions. One case was coded as a suspected suicide attempt and probably represents a coding error.

Among children 6-12 years of age, suicide attempts account for ~85% of hepatic effect cases (39 cases). There were 3 therapeutic error/unintentional misuse cases, 2 intentional abuse cases, and 1 case classified as an adverse drug reaction.

Among those age >12 years, suspected suicide attempts accounted for the majority of hepatic effect cases (~71%) and other intentional reasons for exposure accounted for ~14% of cases. Therapeutic error/unintentional misuse and unintentional general cases each accounted for ~6% of cases. Approximately 0.5% of cases were classified as adverse drug reactions (33 cases).

Figure 9
APAP-Containing Analgesics
Reason for Exposure –Hepatic Effect Cases



Among all age groups there were 853 cases that involved unintentional exposures and 866 cases that involved intentional exposures (excluding suicides) (see Tables 6a and 6b below). There were 20 deaths associated with therapeutic errors and 3 deaths categorized as unintentional unknown. A listing of the 20 therapeutic error cases that provides information on age, gender, medical outcome, reported clinical effects, and substances used is found in Table B10, Appendix B. All of these cases involved subjects >12 years of age. There were 102 deaths associated with intentional reasons for exposure excluding suicides, and the majority of these (61/102) were attributed to intentional misuse. The vast majority of serious cases (i.e., major effects and deaths) with hepatic effects involved subjects >12 years of age even when suicides/suicide attempts were excluded (758/768 cases) (see Tables B7-B9, Appendix B). Although the total number of hepatic effect cases was comparable for the intentional and unintentional reasons for exposure (853 vs. 866), the percentage of cases with hepatic effects (0.48 vs. 3.5%) and the percentage of cases with serious medical outcomes involving hepatic effects (deaths plus major effects) (0.17 vs. 1.52%) was much lower for unintentional reasons for exposure in comparison to intentional reasons for exposure.

There were also a total of 36 cases classified as adverse drug reactions (33 in subjects >12 years of age and 3 in children), including 2 deaths and 16 major effects (see Table B6, Appendix B). However, the information collected by poison control centers in managing

phone calls is typically insufficient to reliably document whether or not the amount taken was truly the recommended therapeutic dose. A listing of these 36 cases classified as adverse drug reactions that provides information on age, gender, medical outcome, reported clinical effects, and substances used is found in Table B11, Appendix B.

Table 6a
APAP-Containing Analgesics
Medical Outcome for Cases Involving Hepatic Effects
Unintentional Exposures

Medical Outcome	Unintentional General	Therapeutic Error	Unintentional Misuse	Unintentional Unknown	Total (% of Total)
Minor Effect	19	12	12	1	44 (0.025)
Moderate Effect	224	89	104	22	439 (0.25)
Major Effect	135	55	77	15	282 (0.16)
Death	0	20	0	3	23 (0.013)
No F/U-Minimally Toxic	4	2	3	1	10 (0.006)
No F/U-Potentially Toxic	18	18	18	1	55 (0.031)
Total Cases with Hepatic Effects	400	196	214	43	853 (0.48)
TOTAL	122607	47929	6870	800	178206

Table 6b
APAP-Containing Analgesics
Medical Outcome for Cases Involving Hepatic Effects
Intentional Exposures (Excluding Suicides)

Medical Outcome	Intentional Misuse	Intentional Abuse	Intentional Unknown	Total (% of Total)
Minor Effect	32	15	7	54 (0.22)
Moderate Effect	220	93	55	368 (1.5)
Major Effect	153	68	52	273 (1.1)
Death	61	17	24	102 (0.42)
No F/U-Minimally Toxic	9	3	1	13 (0.053)
No F/U-Potentially Toxic	36	11	9	56 (0.23)
Total Cases with Hepatic Effects	511	207	148	866 (3.5)
TOTAL	14937	5644	3819	24400

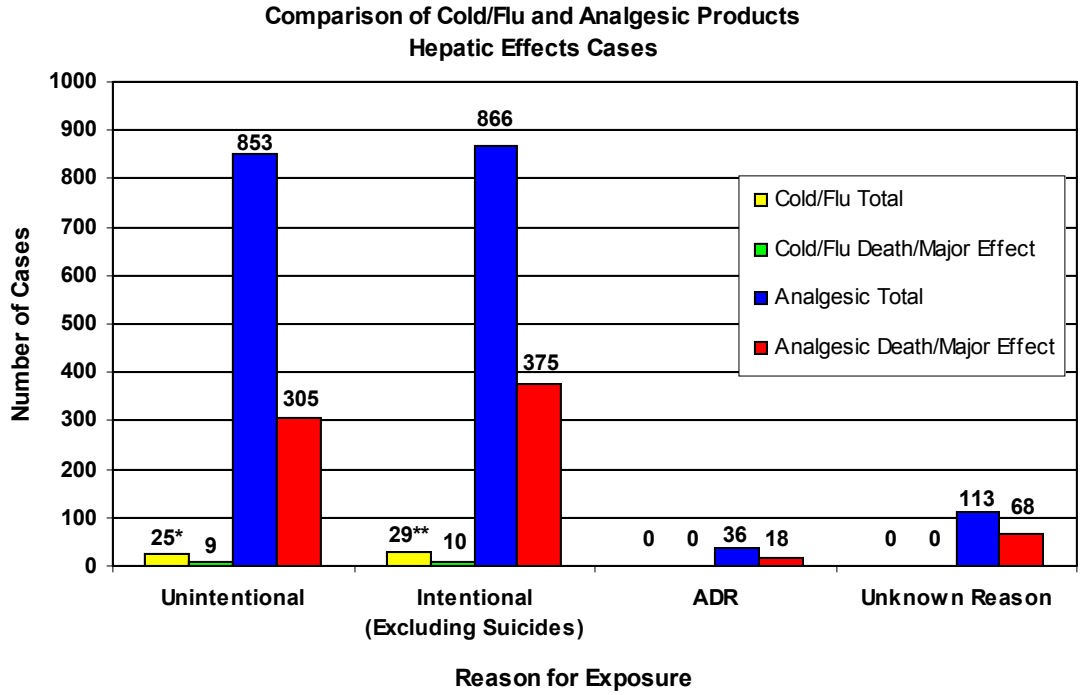
There were a total of 113 cases with an unknown reason for exposure, including 29 deaths and 39 major effects (see Table B6, Appendix B). All of these cases involved subjects >12 years of age. As shown in Table B6, Appendix B, there were also 9 cases with a reason for exposure categorized as "Other" (see definitions in Section 3, Figure 5). These cases included 2 major effects, including one case categorized as Malicious that involved a child under 6 years of age.

4.2.4 Comparison of Hepatic Effect Cases for APAP-Containing Cough and Cold Medications and Analgesics

There were many more hepatic effect cases reported for the APAP-containing analgesics than for the APAP-containing cough and cold products, even when suicide attempts were excluded (see Figure 10 below). This large difference is not accounted for by the difference in the number of total cases reported to poison control centers each year for these two classes of products. The total number of cases reported each year is 5 fold larger for the APAP-containing analgesic data set (~300,000 cases) compared to the APAP-containing cough and cold medications data set (~60,000 cases). However, there is a disproportionately greater

difference in the number of cases with hepatic effects for the analgesic products versus the cough and cold products across all reasons for exposure for both total hepatic effect cases (~34 fold difference) and for hepatic effect cases with serious outcomes, i.e., deaths and major medical outcomes (~40 fold difference). These fold differences would become even larger if duplicate cases (i.e., those found in both data sets because they involved use of both a cough and cold product and an analgesic) were eliminated from the cough and cold products data set (see footnotes to Figure 10 for numbers of duplicate cases).

Figure 10
Comparison of Hepatic Effect Cases
APAP-Containing Cough and Cold Products and Analgesics



*6 of these also involved an analgesic product
**8 of these also involved an analgesic product

4.2.5 Demographics of Cases Involving Hepatic Effects

Age and gender distribution were examined for hepatic effects cases involving unintentional and intentional reasons for exposure (excluding suicides), for adverse drug reactions, and for cases with unknown reason for exposure (see Table 7 below). This analysis was completed only for the year 2000. There appeared to be a trend for more females than males involved across all reasons for exposure, although the magnitude of the gender difference varied among individual categories of reason for exposure.

Table 7
APAP-Containing Analgesics
Demographics for Cases Involving Hepatic Effects
2000

Reason for Exposure	N	Mean Age ± SD (Range)	Gender
Unintentional General	145	28.9 ± 18.9 (1 day – 83 yrs.)	70M/75F
Therapeutic Error	52	46.5 ± 24.9 (1 day – 89 yrs.)	24M/28F
Unintentional Misuse	78	40.2 ± 17.6 (12-89 yrs.)	33M/45F
Unintentional Unknown	17	39.4 ± 27.4 (3 – 87 yrs.)	4M/13F
Total Unintentional	**292**	**ND**	**131M/161F**
Intentional Misuse	189	37.6 ± 16.2 (12 - 85 yrs.)	70M/119F
Intentional Abuse	84	34.9 ± 13.2 (10 – 79 yrs.)	35M/49F
Intentional Unknown	54	37.8 ± 17.7 (13 – 85 yrs.)	23M/31F
Total Intentional*	**392**	**ND**	**128M/199F**
Adverse Drug Reaction	15	39.2 ± 25.2 (7 mo. – 79 yrs.)	5M/10F
Unknown Reason	50	42.8 ± 17.5 (14 – 83 yrs.)	12M/38F

*Excludes suspected suicide attempts
ND – Not Determined

4.2.6 Products Involved in Hepatic Effect Cases - Analgesics (Tables B12a,b-B20a,b, Appendix B)

Tables B12a,b-B20a,b in Appendix B provide a detailed tabulation of the types of products involved in hepatic effects cases for the analgesics data set for the year 2000. The vast majority of cases (85-96%, depending on the reason for exposure) involved the use of only one APAP-containing analgesic product. There did not appear to be a trend for use of more than one APAP-containing product to result in more significant medical outcomes, but the numbers of cases involving more than one product were relatively small. The products used are discussed more thoroughly in Section 4.3 below where the data for hepatic effects cases involving APAP-containing cough and cold medications and/or APAP-containing analgesics are combined in order to evaluate the profile of product use for all APAP-containing products.

4.3 Products Involved in Hepatic Effect Cases – All APAP-Containing Products (Tables 8 and 8a)

A complete picture of hepatic effect cases for the year 2000 for all APAP-containing products (i.e., those found in either the APAP-containing analgesics data set or the APAP-containing cough and cold products data set) is presented in Table 8 below. Duplicate cases (i.e., those that were found in both data sets because they involved both an analgesic and a cough and cold medication) have been eliminated from this table. Across all reasons for exposure (excluding suicide attempts) over 90% of the cases involved the use of only one APAP-containing product, and in 65% of cases the product involved was a single ingredient OTC analgesic. Rx analgesic combination products accounted for 16% of cases across all reasons for exposure. Intentional abuse cases showed a higher percentage of cases involving an Rx combination analgesic (33%) and a lower percentage of cases involving a single ingredient OTC analgesic (42%) compared to all other reasons for exposure. Use of an APAP-containing OTC cough and cold product as the only APAP-containing product accounted for 2% of all cases. Less than 10% of cases involved concomitant use of more than one APAP-containing product. Among those cases, the concomitant use of a single ingredient OTC analgesic plus an Rx analgesic combination product was the most frequently reported (4% of cases). Two percent of cases (18 cases) involved the use of any two OTC APAP-containing products. The types of OTC products involved in these cases are shown in Table 8a. One percent of cases involved the use of two Rx analgesic combination products. Less than 1% of cases involved the use of three or more APAP-containing products, and none of these cases involved unintentional exposures.

Table 8
Acetaminophen-Containing Products Used in Cases With Hepatic Effects
2000

	No. of Cases (% of Cases)				**No. of Cases (% of Cases)**				**No. of Cases (% of Cases)**	
Reason for Exposure	**One APAP Product**				**Two APAP Products**				**Three or More APAP Products**	**Total**
	Single Ingredient OTC Analgesic	Rx Analgesic Combo	OTC Combo Not Cough/Cold	OTC Combo Cough/Cold	OTC Analgesic + Rx Analgesic Combo	Any Two OTC Products	Rx Analgesic Combo + Any OTC Combo	Two Rx Analgesic Combos	Any Three or More Products	
Unintentional General	103 (70%)	16 (11%)	16 (11%)	2 (1%)	6 (4%)	1 (<1%)	0	3 (2%)	0	147
Therapeutic Error	34 (61%)	9 (16%)	1 (2%)	3 (5%)	6 (11%)	1 (2%)	2 (4%)	0	0	56
Unintentional Misuse	55 (68%)	6 (7%)	7 (8%)	3 (4%)	5 (6%)	5 (6%)	0	0	0	81
Unintentional Unknown	13 (76%)	2 (12%)	1 (6%)	0	0	1 (6%)	0	0	0	17
Subtotal Unintentional	**205 (68%)**	**33 (11%)**	**25 (8%)**	**8 (3%)**	**17 (6%)**	**8 (3%)**	**2 (<1%)**	**3 (2%)**	**0**	**301**
Intentional Misuse	136 (72%)	28 (15%)	7 (4%)	0	8 (4%)	5 (3%)	1 (<1%)	2 (1%)	2 (1%)	189
Intentional Abuse	37 (42%)	29 (33%)	9 (10%)	5 (6%)	2 (2%)	3 (3%)	1 (1%)	2 (2%)	1 (1%)	89
Intentional Unknown	34 (63%)	9 (17%)	6 (11%)	0	0	2 (4%)	1 (2%)	1 (2%)	1 (2%)	54
Subtotal Intentional	**207 (62%)**	**66 (20%)**	**22 (7%)**	**5 (1.5%)**	**10 (3%)**	**10 (3%)**	**3 (1%)**	**5 (1.5%)**	**4 (1%)**	**332**
Adverse Drug Reaction	12 (80%)	2 (13%)	0	0	0	0	0	1 (7%)	0	15
Unknown	31 (62%)	10 (20%)	7 (14%)	0	0	0	0	0	2 (4%)	50
Total	**455 (65%)**	**111 (16%)**	**54 (8%)**	**13 (2%)**	**27 (4%)**	**18 (3%)**	**5 (<1%)**	**9 (1%)**	**6 (<1%)**	**698**

Table 8a
Acetaminophen-Containing Products Used in Cases with Hepatic Effects That Involved Two OTC Products (Expanded From Table 8)

	Number of Cases						
Reason for Exposure	Two Single Ingredient OTC Analgesics	Single Ingredient OTC Analgesic + APAP/Other Active Combo*	Single Ingredient OTC Analgesic + APAP/ASA Plus Other Active Combo**	APAP/Other Active Combo + APAP/ASA Plus Other Active Combo	Single Ingredient OTC Analgesic + OTC Cough/Cold Combo	Two OTC Cough/Cold Combos	Total
Unintentional General	1	0	0	0	0	0	1
Therapeutic Error	0	0	0	0	0	1	1
Unintentional Misuse	1	3	0	0	1	0	5
Unintentional Unknown	0	0	0	0	1	0	1
Subtotal Unintentional	**2**	**3**	**0**	**0**	**2**	**1**	**8**
Intentional Misuse	1	0	1	1	2	0	5
Intentional Abuse	0	0	3	0	0	0	3
Intentional Unknown	0	0	1	1	0	0	2
Subtotal Intentional	**1**	**0**	**5**	**2**	**2**	**0**	**10**
Total	**3**	**3**	**5**	**2**	**4**	**1**	**18**

*APAP/Other Active Combo – A common example of products in this category is an APAP/Diphenhydramine (i.e., Analgesic/Sleep Aid) combo.
**APAP/ASA Plus Other Active Combo – A common example of products in this category is an APAP/Aspirin/Caffeine combination product

4.4 Cough and Cold Medications Without Analgesic

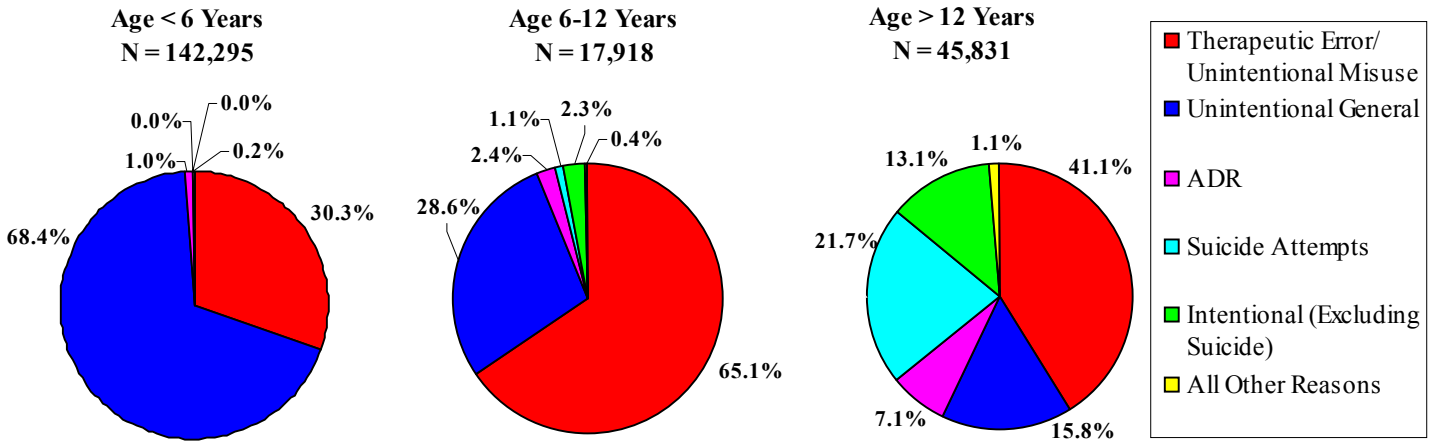
Data for cough and cold products without an analgesic were analyzed and compared to the data for the APAP-containing cough and cold products in order to assess the relative contribution of the presence of APAP to the overall profile of toxicity for the latter. The cough and cold products without an analgesic typically contain the same types of active ingredients (e.g., decongestant, antihistamine, antitussive, expectorant) as the APAP-containing cough and cold combinations except that they do not contain APAP, aspirin, or any other analgesic.

4.4.1 Medical Outcome and Reason for Exposure – All Cases (Tables C1-C4, Appendix C)

There were a total of ~65,000-70,000 reports per year for products included in this data set resulting in a total of over 200,000 cases over the three year period. Similar to the APAP-containing cough and cold medications, the majority of cases involved no clinical effects (~29%), minor effects (~14%), or received no or minimal follow-up because the quantities ingested were expected to result in no or minimal clinical effects (~49%). Serious medical outcomes (i.e., major effects and deaths) accounted for ~0.2% of cases, and the majority of these (~72%) were associated with intentional exposures, predominantly suicide attempts (see Table C1, Appendix C). These findings are comparable to the profile for the APAP-containing cough and cold products where ~0.3% of cases involved serious medical outcomes (see Section 4.1.1).

The profile of reasons for exposure for the three different age ranges evaluated (see Figure 11 below and Tables C2-C4, Appendix C) was generally comparable to the APAP-containing cough and cold medications (see Section 4.1.1). Among children <6 years of age, unintentional general cases (i.e., accidental ingestions) predominated (~68% of cases), and therapeutic error/unintentional misuse accounted for most of the remaining cases (~30%). Among children 6-12 years of age, therapeutic errors/unintentional misuse were the most frequently reported reason (~65%), and unintentional general cases were the second most frequently reported reason (~29%). Among those age >12 years, therapeutic errors/unintentional misuse were more frequently reported for the cough and cold medications without analgesic compared to the APAP-containing cough and cold medications (~41% vs. ~29%), and suicide attempts were less frequently reported (~22% vs. ~32%) (see Figure 6, Section 4.1.1 and Figure 11 below).

Figure 11
Cough and Cold Medications Without Analgesic
Reason for Exposure – All Cases



4.4.2 Clinical Effects – All Cases (Table C5, Appendix C)

The total number of clinical effects reported by body system was evaluated by broad category of reason for exposure (i.e., unintentional, intentional, adverse drug reaction, other, unknown) and is summarized in Table 9 below. Only clinical effects judged by the poison control center to be related or of unknown relationship to the exposure were counted. Clinical effects judged by the poison control center to be not related to the exposure were excluded. For hepatic/hematological effects, only those effects that were reported in cases that did not involve concomitant exposure to an APAP-containing product were included. Cases that involved concomitant exposure to an APAP-containing product were excluded. The latter cases are captured in one or both of the other two data sets evaluated in this report.

The most frequently reported clinical effects for the cough and cold medications without analgesic were similar to those reported for the APAP-containing cough and cold medications (see Section 4.1.2). These included drowsiness/lethargy (14.2% of cases), agitation/irritability (3.1%), tachycardia (2.6%), vomiting (2.1%), and dizziness/vertigo (1.8%) (see Table C5, Appendix C). Hepatic effects were extremely rare and were reported in only 13 cases (0.006%) after excluding cases that also involved an APAP-containing product (see Table C6, Appendix C).

Table 9
Cough and Cold Medications Without Analgesic
Summary of Clinical Effects by Reason for Exposure
1998-2000 - All Ages

	Number of Clinical Effects					
Body System	**Unintentional (N=183868 Cases)**	**Intentional* (N=16860 Cases)**	**Adverse Drug Reaction (N=5052 Cases)**	**Other (N=348 Cases)**	**Unknown (N=300 Cases)**	**Total (N=206428 Cases)**
Cardiovascular	2582	5339	536	13	51	8521
Dermal	728	246	1029	1	11	2015
Gastrointestinal	4827	3111	817	11	32	8798
Hepatic/Hematological**	1	13	5	0	0	19
Neurological	34012	9576	2605	30	168	46391
Ocular	1582	975	193	3	15	2768
Renal	43	82	32	0	2	159
Respiratory	333	319	186	1	10	849
Miscellaneous	3561	1801	941	11	29	6343
Total Number of Clinical Effects	**47672**	**21536**	**6344**	**70**	**321**	**75943**

*Includes suspected suicide attempts
** Excludes cases that involved concomitant exposure to an APAP-containing product

4.4.3 Medical Outcome and Reason for Exposure - Hepatic Effect Cases (Table C6-C7, Appendix C)

Although not expected with cough and cold medications without analgesic, 13 cases involving hepatic effects were reported after excluding cases with concomitant use of an APAP-containing product (Table C6, Appendix C). Approximately half of these (6/13) involved suspected suicide attempts. A listing of the 7 remaining cases involving hepatic effects that provides information on age, gender, medical outcome, reason for exposure, reported clinical effects, and substances used is found in Table C7, Appendix 3. These 7 cases included 2 deaths classified as intentional abuse cases and 1 major medical outcome

classified as an adverse drug reaction. All three of these cases involved concomitant use of another drug which probably contributed to the major effect outcome or death.

5. Discussion and Conclusions

The use of AAPCC TESS data to evaluate post-marketing reports of hepatotoxicity associated with the use of APAP-containing products provides a valuable source of information to address questions related to the root causes of these incidents. The AAPCC TESS database includes all calls made to phones serving the general public at all poison control centers participating in TESS. Based on information provided in the annual reports published by the AAPCC, these poison control centers serve approximately 96% of the US population (References 1-3).

One advantage offered by the AAPCC TESS data in addressed questions related to APAP-related hepatotoxicity incidents is the use of standardized definitions of reasons for exposure and medical outcome by all participating poison control centers. Another advantage is that the AAPCC TESS database includes all incidents that involve a call to a public phone number at a poison control center and therefore is not dependent upon voluntary reporting of the incident to the FDA or to the manufacturer.

Limitations of the AAPCC TESS data must also be considered. As with other post-marketing spontaneous adverse event reports, the accuracy of the information on each AAPCC TESS case is dependent upon the person calling the poison control center. The caller may be the subject involved in the incident, a family member, a child care provider, a health care professional involved in treating the subject, etc. Another limitation is that information on the quantity of a drug or other substance that has been consumed is not available via the standard report format provided by the AAPCC TESS. From the AAPCC TESS definitions of reason for exposure, it can be assumed that adverse drug reactions involve the use of the recommended therapeutic dose, and all other unintentional and intentional reasons for exposure involve the use of more than the recommended therapeutic dose. However, the classification of each case remains dependent upon the information provided by the caller, which may or may not be accurate. Furthermore, although a judgment is made by the poison control center staff regarding whether the clinical effects reported by the caller are related, not related, or of unknown relationship to the reported exposure, the information collected by poison control centers is typically insufficient to conduct a thorough assessment of causality ruling out other possible causes. Nevertheless, despite these limitations, which are common to most post-marketing surveillance systems, an analysis of the AAPCC TESS data for APAP-containing products provides information that is important to consider in determining how cases of APAP-associated hepatotoxicity might be reduced.

Several observations can be made from the data presented in this report. First, the vast majority of reported cases involved an APAP-containing analgesic product. APAP-containing cough and cold medications were not an important contributor to poison control center reports of APAP-associated hepatotoxicity.

In depth analysis of products involved in cases reported in the year 2000 indicates that concomitant use of more than one APAP-containing product was not a major root cause of incidents involving hepatotoxicity. Most cases (>90%) involved a single product, most frequently an OTC analgesic (65% of cases). APAP-containing Rx combination analgesics were the second most frequently reported product category (16% of cases). Less than 10% of cases involved concomitant use of more than one APAP-containing product. Among those cases, the concomitant use of a single ingredient OTC analgesic plus an Rx combination analgesic was the most frequently reported (4% of cases). These data indicate that there are few incidents of hepatotoxicity associated with multisymptom cough and cold medications containing APAP even when considering the scenario of the use of more than one APAP-containing product.

During the three year period evaluated there were no reported cases involving hepatic effects with the use of an APAP-containing cough and cold medication as recommended. Such cases would have been classified as adverse drug reactions according to AAPCC TESS definitions, and none of these were reported. There were a small number of adverse drug reactions with hepatic effects reported for the APAP-containing analgesic products (36 cases representing 0.01% of total cases). However, insufficient information is available on these cases to conduct a thorough assessment of causality ruling out other possible causes or to reliably document whether or not the amount of APAP take was truly within the recommended therapeutic dose.

A comparison of the APAP-containing cough and cold medications with the cough and cold medications without analgesic indicates that both of these sets of products present quite benign profiles with respect to medical outcomes and clinical effects. Although the presence of APAP in cough and cold medications was associated with some reports involving hepatotoxicity, these were rare in comparison with the APAP-containing analgesics. A small number of cases involving hepatic effects was also reported for the cough and cold medications that do not contain an analgesic, a finding which was unexpected based on the ingredients found in these products. This could be attributable to the concomitant use of other drugs or to other factors that cannot be explored due to the limitations discussed previously that preclude a thorough assessment of causality.

Taken as a whole, these data indicate that cases of hepatotoxicity associated with APAP-containing products result from the intentional or unintentional incorrect use of these products. Cases involving hepatic effects with recommended therapeutic use are very rare and impossible to confirm given the limitations inherent in data collection. Intentional or unintentional incorrect use of these products can be addressed by labeling changes and by public education programs that inform consumers about products containing APAP and the potential for serious consequences associated with overdosing.

REFERENCES

1. Litovitz TL, Klein-Schwartz W, Caravati EM, Youniss J, Crouch B, and Lee S. 1998 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 17:435-487 (1999)

2. Litovitz TL, Klein-Schwartz W, Shite S, Cobaugh DJ, Youniss J, Drab, A, and Benson BE. 1999 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 18:517-574 (2000)

3. Litovitz TL, Klein-Schwartz W, White S, Cobaugh D, Youniss J, Omslaer JC, Drab A, and Benson BE. 2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med. 19:337-395 (2001)