

MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT          OPDRA SAFETY REVIEW  
                         Review of Acetaminophen Poisoning Exposures in Toxic  
                         Exposure Surveillance System (TESS)

**Executive summary:**

The Toxic Exposure Surveillance System or TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of poison control centers in the U.S. The AAPCC's annual reports from 1995-1999 which summarize the TESS data were reviewed to determine the extent of poisoning in association with exposure to acetaminophen products.

Acetaminophen is a pharmaceutical agent commonly associated with poisoning in the U.S. In the five-year review period, the overall number of calls to poison control centers concerning acetaminophen exposures has declined slightly from 111,175 in 1995 to 108,102 in 1999. However, the number of fatalities in association with acetaminophen exposures has increased by nearly 100 per cent from 76 in 1995 to 141 in 1999. Overall, acetaminophen fatalities represented 16% of the total 873 fatalities that were reported in the TESS database in 1999. Approximately 50% of acetaminophen-associated fatalities occurred in individuals who took single-ingredient acetaminophen products which are available over-the-counter (OTC). The remaining fatalities occurred in individuals who took acetaminophen combination products including butalbital, or diphenhydramine, or aspirin or aspirin/caffeine, or narcotics namely hydrocodone, oxycodone, codeine or propoxyphene. Most of these combination products are prescription products. In 1999, there were 11 (8%) fatalities in which multiple acetaminophen-containing products were ingested. In five cases an OTC acetaminophen product was taken concomitantly with a prescription acetaminophen product. In three cases two prescription acetaminophen products were involved. In two cases three different acetaminophen-containing products including two prescription-only formulations were ingested. In one case an OTC single-

ingredient acetaminophen product and an OTC acetaminophen/diphenhydramine combination product were taken simultaneously. Of the 141 fatalities in association with acetaminophen reported to TESS in 1999, fifty-five percent or 77 of the cases had suicidal intent, and 8% were unintentional. Other or unknown reasons accounted for the remaining 37% of the cases.

Overall, 37% of all acetaminophen exposures documented by TESS in 1999 occurred in children under 6 years old, 22% in children and adolescents between the ages of 6 and 19 years old, and 38% in adults over 19 years. Age was unknown in 3% of the acetaminophen exposures. Thirty-four percent of children up to the age of 19 years were taking adult formulations of acetaminophen. At least 22% of children under 6 years of age used adult formulations.

In 1999, there were 108,102 exposures reported to TESS with acetaminophen and this represents 10% of 1,020,598 exposures reported with all pharmaceutical substances. Deaths in association with acetaminophen have increased by nearly 100 percent from 76 in 1995 to 141 in 1999. Overall, deaths with acetaminophen represent 16% of the total 873 deaths reported to TESS in 1999. Thirty-seven percent (40,105) of acetaminophen exposures occurred in children < 6 years of age and 22% (23,689) in children and adolescents between 6 and 19 years old. Seventy-six percent (82,062) of exposures were related to OTC acetaminophen products and the remainder largely to acetaminophen-narcotic combination products that are available by prescription. Of the 141 acetaminophen-related fatalities reported in 1999, fifty-five percent of the cases had suicidal intent, and 8% were unintentional. Other or unknown reasons accounted for the remaining 37% of the fatalities.

### **Background and Methods:**

The Toxic Exposure Surveillance System or TESS is a poisoning surveillance database maintained by the American Association of Poison Control Centers (AAPCC) in cooperation with 64 poison control centers in the U.S.<sup>1</sup> In 1999 (the latest year for which we have data), poison control centers linked with AAPCC served nearly 261 million of the U.S. population. Since 1983 when TESS was started, to the present time, this database contains 27 million potential human poison exposure cases including 2.2 million cases reported in 1999 alone.<sup>2</sup> The 1999 data represent an estimated 96% of the potential human poison exposures that precipitated poison center contacts in the U.S.

The AAPCC's annual reports from 1995-1999 summarize TESS data and were reviewed to determine the extent of poisoning in association with exposure to acetaminophen products. Only those cases were included that listed acetaminophen as the primary (first) agent. Two tables in the annual reports (Table 21: Summary of Fatal exposures, and Table 22B: Demographic Profile of Exposure Cases by Generic Category of Substances and Products) were reviewed and formed the basis of this report.

## Definitions and terminology used:

In the annual reports, '*major effect*' is defined as signs or symptoms occurring as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement. '*Death*' is when a patient dies as a result of the exposure or as a direct complication of the exposure. Only those deaths that are probably or undoubtedly related to the exposure are coded in TESS.

The various reasons for exposure are defined here. '*Intentional misuse*' is an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. '*Intentional abuse*' is an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect. All recreational use of substances for any effect is included. '*Intentional unknown*' is an exposure that is determined to be intentional but the specific motive is unknown. '*Unintentional unknown*' is an exposure determined to be unintentional but the exact reason is unknown. '*Unintentional general*' includes all unintentional exposures not specifically defined. '*Adverse reaction*' is defined as an adverse event occurring with normal, prescribed, labeled or recommended use of the product, as opposed to overdose, misuse or abuse. Included are cases with an unwanted effect caused by an allergic, hypersensitive, or idiosyncratic response to the active ingredients, inactive ingredients, or excipients. Concomitant use of a contraindicated medication or food is excluded, and coded instead as a therapeutic error. '*Therapeutic error*' is defined as 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. '*Suspected suicidal*' is defined as an exposure resulting from the inappropriate use of a substance for reasons that are suspected to be self-destructive or manipulative.

*Acute exposure* is defined as a single, repeated or continuous exposure occurring over a period of 8 hours or less. *Chronic exposure* is defined as a continuous, repeated or intermittent exposure to the same substance in a period exceeding 8 hours.

*Acute-on-chronic* is defined as a single exposure preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours.

For 1999, in summarizing the reasons for acetaminophen intake in cases which resulted in fatalities, we combined the categories of *unintentional unknown*, *therapeutic error*, and *intentional misuse* in a general category as 'Unintentional' (Table 7). We included *intentional misuse* since these were not classified as suicides, and were assumed likely to represent individuals who ingested excessive acetaminophen with therapeutic intent, such as pain or fever relief.

Health care facilities include acute care hospitals, physician offices or clinics, and freestanding emergency centers. Nonhealth care facility refers to the site of exposure that is usually the patient's home.

**Results:**

Table 1 gives the comparison of 5-year acetaminophen exposures by number and types of formulations including either adult or pediatric, and single ingredient or combinations.<sup>2-6</sup> There is a little variation in the number of exposures over the 5-year period. In the 1995 calendar year, 111,175 acetaminophen exposures alone or in combination with other products (including narcotics, butalbital, aspirin, and diphenhydramine) were recorded in the TESS database. In 1999, acetaminophen exposures declined to 108,102, representing 10% of 1,020,598 exposures reported with all pharmaceutical substances in TESS.

**Table 1: Number and Type of Acetaminophen Exposures as Reported in TESS**

Year	# of exposures – APAP only			# of exposures – APAP in combination with							
	Adult preps	Ped. preps	Unknown	ASA + Others	ASA only	Codeine	Oxycodone	Propoxyph	Other narcotics	Other drugs Adult preps	Other Ped.
1999	25,978	26,151	8,963	5,423	12	5,741	3,553	5,120	11,626	15,213	322
1998	26,768	30,759	9,358	4,630	19	6,237	3,480	5,333	10,341	14,475	54
1997	28,480	32,917	11,183	3,672	30	7,254	3,639	6,094	10,975	15,510	53
1996	28,896	34,729	9,322	3,085	33	6,940	3,189	5,311	8,551	13,752	75
1995	27,586	36,106	9,197	2,621	26	7,108	2,853	5,180	7,878	12,401	219

APAP = Acetaminophen; Ped. = Pediatric; ASA = Aspirin; Propoxyph = Propoxyphene

*Single ingredient adult formulations of acetaminophen:* In 1999, of the 25,978 exposures to adult formulations of single-ingredient acetaminophen products, 37% occurred in adults over 19 years old, almost 35% in children between the ages of 6 and 19 years of age, and nearly 25 percent in children less than 6 years of age. About half (51%) of poison exposures were unintentional and 48% were intentional. Fifty-six per cent of the cases were treated in a health care facility and 2% of all cases suffered major effects or death as an outcome.

*Single ingredient pediatric formulations of acetaminophen:* In 1999, of the 26,151 exposures to pediatric formulations of single-ingredient acetaminophen products, nearly 90% occurred in children under 6 years of age and about 9% in children between 6 and 19 years of age. Ninety-eight percent of the exposures were unintentional. About 88% of the cases were managed in a non-healthcare facility usually at the site of exposure, the patient's own home. In contrast, only 12% were managed in a health care facility. Twenty-two cases had a major effect but no death was recorded in this group.

*Acetaminophen in combination with aspirin and other ingredients (excluding narcotics):* In 1999, of the 5,423 exposures, 32% occurred in adults over 19 years old; 27% in children between 6 and 19 years; and 37% in children under 6 years old. Fifty-seven percent of the exposures were unintentional and 38% intentional. The remaining 5% included adverse reactions, other or unknown. Forty-five percent of the cases were managed in a health care facility. Twenty-two cases had a major effect and 4 deaths were recorded in this group.

*Acetaminophen in combination with narcotics including codeine, oxycodone, and propoxyphene (total combined):* In 1999, there were 26,040 exposures in this combined group, of which exposure to codeine, propoxyphene, oxycodone, or other narcotics products were 22% (5,741), 20% (5,120), 14% (3,553), and 45% (11,626) respectively. Sixty-six percent were adults >19 years; 15% were children between 6 and 19 years; and 13% were under 6 years of age. Fifty-three percent of the exposures were intentional and about 40% unintentional. The remaining 7% included adverse reactions and others. The majority of patients (56%) were managed in a health care facility and 76 deaths were recorded.



*Acetaminophen in combination with other drugs including butalbital, caffeine and diphenhydramine:* In 1999, of the 15,535 exposures with combined adult and pediatric formulations in this category, about 16% occurred in children under 6 years of age, and about 25% in children between 6 and 19 years old. Thirty-six percent of the exposures were unintentional and about 60% intentional. The remaining 4% included adverse reactions and others. About 63% of the cases were managed in a health care facility and 2% had major outcomes. There were 12 deaths recorded in this category.

Table 2 summarizes 1999 acetaminophen exposures by type of formulation, and gives a breakdown by intentionality, by number treated in a health care facility, and by major effect. Fifty-eight percent of all acetaminophen exposures reported in 1999 were unintentional in nature and 46% of all cases were treated in a health care facility. Two percent of these cases had major effect. It is possible that a single case may have received treatment in a health care facility, resulting in major effect and ultimately death.

**Table 2: Acetaminophen Exposures by Motive, Type of Formulation, Treatment and Major Outcome 1999**

Type of Acetaminophen	Total	Unintentional (% of row)	Treated in HCF (% of row)	Major Effect
Single Ingredient APAP				
Adult form	25,978	13,257 (51)	14,610 (56)	457 (2)
Ped. Form	26,151	25,694 (98)	3,075 (12)	22
Unknown form	8,963	4,342 (48)	5,237 (58)	261 (3)
Total	61,092	43,293 (71)	22,922 (37)	740 (1)
APAP Combo				
w/ASA etc.	5,423	3,096 (57)	2,432 (45)	22
w/ASA only	12	7 (58)	4 (33)	0
Total	5,435	3,103 (57)	2,436 (45)	22
APAP w/others	15,535	5,672 (36)	9,745 (63)	314 (2)
APAP Combo w/narcotics	26,040	10,254 (17)	14,624 (24)	692 (3)
Grand Total	108,102	62,322 (58)	49,727 (46)	1,768 (2)

HCF = Health Care Facility; APAP = Acetaminophen; ASA = Aspirin; Ped. = Pediatric; OTC = Over The Counter;

According to the 1999 Annual Report of AAPCC, 873 fatal poisonings were reported and pharmaceutical agents were the primary substances involved in 64% of these fatalities. Acetaminophen, aspirin, and other salicylates caused more than 70% of analgesic-related fatalities in that year.

Table 3 summarizes 1999 acetaminophen exposures by type of formulation and gives an age breakdown. Overall, thirty-seven percent of acetaminophen exposures occurred in children under 6 years old, 22% in children and adolescents between the ages of 6 and 19 years old, and 38% in adults over 19 years. Age was unknown in 3% of the acetaminophen exposures. Of the 63,794 children less than or equal to 19 years, at least 34% used adult formulations. At least 22% of children < 6 years of age used adult formulations of acetaminophen. Data were not available to determine these percentages by intentionality.

**Table 3: Acetaminophen Exposures By Type and Age in 1999**

Type of Product	Age (years)				Unknown (%)
	< 6 (%)	6-19 (%)	>19 (%)		
Single ingredient APAP					
Adult formulation	25,978	6,412 (10)	9,084 (15)	9,657 (16)	825
Ped. Formulation	26,151	23,324 (38)	2,508 (4)	273	46
Unknown	8,963	2,572 (4)	2,852 (5)	3,222 (5)	317
Total	<b>61,092</b>	<b>32,308 (53)</b>	<b>14,444</b>	<b>13,152</b>	<b>1,188</b>
APAP w/OTC Combo					
ASA + others	5,423	2,016 (37)	1,476 (27)	1,756	175
ASA only	12	5	3	4	0
Total	<b>5,435</b>	<b>2,021 (37)</b>	<b>1,479</b>	<b>1,760</b>	<b>175</b>
APAP w/Narcotics Rx	<b>26,040</b>	<b>3,330 (13)</b>	<b>3,946 (15)</b>	<b>17,197 (66)</b>	<b>1,567 (6)</b>
APAP in combo					
w/Other drugs-Adult	15,213	2,222	3,760	8,528	703
w/Other drugs-Ped	322	224	60	34	4
Total	<b>15,535</b>	<b>2,446 (16)</b>	<b>3,820</b>	<b>8,562</b>	<b>707</b>
Grand Total	<b>108,102</b>	<b>40,105 (37)</b>	<b>23,689 (22)</b>	<b>40,671 (38)</b>	<b>3,637 (3)</b>

APAP = Acetaminophen; ASA = Aspirin; Ped. = Pediatric; OTC = Over The Counter; Rx = Prescription

Tables 4, 5, and 6 give the comparison of 5-year (1995 to 1999) fatal exposures to acetaminophen as single-ingredient over-the-counter (OTC) products, OTC acetaminophen combination products, and prescription acetaminophen combination products. There is very little variation in the median and mean ages over the past 5 years. However, the number of reported fatal exposures has increased by nearly 100 per cent from 76 in 1995 to 141 in 1999. In 1999, about 49% of acetaminophen-associated fatalities occurred in individuals who took single-ingredient acetaminophen. About 9% of the fatalities occurred in individuals who took OTC acetaminophen combination products containing mainly diphenhydramine or aspirin and/or caffeine. The remaining 42% of the fatalities occurred in those who took prescription acetaminophen-containing products mainly narcotics including hydrocodone, oxycodone, codeine, or propoxyphene.

In 1999, there were 11 (8%) fatalities in which multiple acetaminophen-containing products were ingested. These cases are captured in Tables 4-7. In five cases an OTC acetaminophen product was taken concomitantly with a prescription acetaminophen product. In three cases two prescription acetaminophen products were involved. In two cases three different acetaminophen-containing products including two prescription-only formulations were ingested. In one case an OTC single-ingredient acetaminophen product and an OTC acetaminophen/diphenhydramine combination product were taken simultaneously. Six of the 11 individuals took acetaminophen with suicidal intent, 4 were unintentional users, and the intention was unknown in the remaining case.

**Table 4: Fatalities in Association with OTC Single-ingredient Acetaminophen Products**

	1999	1998	1997	1996	1995
Age (years)	Range 12-97 Median 41 Mean 45	Range 17-87 Median 42 Mean 45	Range 2-84 Median 41 Mean 43	Range 11-80 Median 40 Mean 39	Range 1-71 Median 36 Mean 37
Total cases	68	57	49	41	41
Exposure type	A-31; C-23; A/C-6; U-8	A-29; C-12; A/C-2; U-14	A-18; C-13; A/C-7; U-11	A-19; C-12; A/C-2; U-8	A-8; C-20; A/C-1; U-12
Route	Ing-67; Ing/Inh/Par-1	Ing-57	Ing-49	Ing-41	Ing-39; Ing/Paren-2
Reason	Int. suicide-33; Int. misuse-18; Ther error-9; Unk-3; Int Unk-2; Int abuse-2; Adr-1	Int. suicide-35; Int. misuse-4; Ther error-6; Unk-9; Int unk-2; Unint unk-1	Int. suicide-23; Int. misuse-8; Ther error-9; Unk-6; Int unk-2; Unint unk-1	Int. suicide-14; Int. misuse-6; Ther error-8; Int unk-4; Unk-7; Int. abuse-2;	Int. suicide-20; Int. misuse-6; Ther error-7; Int unk-6; Unk-2

A=Acute; C=Chronic; A/C= Acute on Chronic; U=Unknown; Ing=Ingestion; Inh=Inhalation; Par=Parenteral; Int.=Intentional; Ther=Therapeutic; Unk=Unknown; Adr=Adverse reaction; Unint=Unintentional;

**Table 5: Fatalities in Association with OTC Acetaminophen Combination Products**

	1999	1998	1997	1996	1995
Age (years)	Range 21-46 Median 37 Mean 35	Range 19-90 Median 40 Mean 42	Range 29-43 Median 40 Mean 37	Range 38-76 Median 44 Mean 49	Range 15-81 Median 28 Mean 36
Total cases	12	13	3	7	8
APAP Combos With	ASA-1; ASA/Caffeine-1; Diphen-10	Diphen-13	Dextro/Pseudo/Do xylamine-1; Diphen-2	Diphen-7	Diphen-7; ASA/Caffeine-1
Exposure type	A-8; A/C-2; U-2	A-11; A/C-1; U-1	A-2; A/C-1	A-3; C-2; U-2	A-5; A/C-1; U-2
Route	Ing-12	Ing-13	Ing-3	Ing-7	Ing-7; Ing/Inh-1
Reason	Int. suicide-11; Int. misuse-1	Int. suicide-13	Int. suicide-3	Int. suicide-4; Int. misuse-1; Unk-1; Unint. Misuse-1	Int. suicide-7; Int unk-1

A=Acute; C=Chronic; A/C= Acute on Chronic; U=Unknown; Ing=Ingestion; Inh=Inhalation; Par=Parenteral; Int.=Intentional; Ther=Therapeutic; Unk=Unknown; Adr=Adverse reaction; Unint=Unintentional; Caff=caffeine; Hydrocod=hydrocodone; Oxycod=oxycodone; Propoxyph=propoxyphene; ASA=Aspirin; Diphen=Diphenhydramine; Pseudo=pseudoephedrine; Dextro=dextromethorphan

**Table 6: Fatalities in Association with Prescription Acetaminophen Combination Products**

	1999	1998	1997	1996	1995
Age (years)	Range 12-97 Median 41 Mean 45	Range 23-86 Median 44 Mean 46	Range 14-88 Median Mean 46	Range 22-78 Median 40 Mean 44	Range 34-88 Median 43 Mean 46
Total cases	61	51	46	33	27
APAP-combos with	Butalbital/Caff/Codeine-1; Codeine-1; Hydrocod-34; Oxycod-12; Propoxyph-13;	Codeine-8; Hydrocod-21; Oxycod-4; Propoxyph-18	Codeine-5; Hydrocod-14; Oxycod-2; Propoxyph-23; Pentazocine-1; Isometheptene/dichlorphenazone-1	Codeine-7; Hydrocod-9; Oxycod-2; Propoxyph-9; Butalbital/caffeine-5; Opiate-1	Codeine-4; Hydrocod-4; Oxycod-3; Propoxyph-15; Butalbital/caffeine-1
Exposure type	A-23; C-11; A/C-19; U-8	A-17; C-12; A/C-15; U-7	A-21; C-7; A/C-13; U-5	A-13; C-8; A/C-8; U-4	A-12; C-4; A/C-5; U-6
Route	Ing-60; Ing/Unk-1	Ing-51	Ing-45; Ing/Inh-1	Ing-32; Ing/Unk-1	Ing-27
Reason	Int. suicide-33; Int. misuse-14; Unk-3; Int Unk-6; Int abuse-5	Int. suicide-35; Int. misuse-4; Ther error-3; Unk-1; Int unk-4; Int. abuse-4	Int. suicide-28; Int. misuse-5; Ther error-3; Unk-4; Int. unk-3; Int. abuse-2; Adr-1	Int. suicide-19; Int. misuse-3; Ther error-1; Unk-4; Int unk-2; Int. abuse-3; Unint unk-1;	Int. suicide-19; Int. misuse-3; Int unk-1; Unk-3; Adr-1

A=Acute; C=Chronic; A/C= Acute on Chronic; U=Unknown; Ing=Ingestion; Inh=Inhalation; Par=Parenteral; Int.=Intentional; Ther=Therapeutic; Unk=Unknown; Adr=Adverse reaction; Unint=Unintentional; Caff=caffeine; Hydrocod=hydrocodone; Oxycod=oxycodone; Propoxyph=propoxyphene;

Ingestions accounted for the main route of exposure in most years. Acute exposures comprised the majority of cases in most years followed by chronic exposure, and acute on chronic or unknown.

Table 7 summarizes the reasons cited for acetaminophen fatalities in 1999. Of the 141 fatalities in association with acetaminophen reported to TESS in 1999, fifty-five percent of the cases had suicidal intent, and 8% were unintentional. Other or unknown reasons accounted for the remaining 38% of the cases.

**Table 7: Reasons Cited for Acetaminophen Intake in Fatal Cases in 1999**

APAP Formulation	Suicidal Intent	Unintentional	Others/Unknown	Total
Single ingredient-OTC	33	10	25	68
Combo-OTC	10	0	1	11
Rx-Combo	28	1	22	51
Multiple APAP products	6	4	1	11

**Acknowledgement**

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