

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

DATE: August 15, 2002

TO: Charles Ganley, M.D., Director
Division of OTC Drugs, HFD-560

THROUGH: Julie Beitz, M.D., Director *Beitz 8/15/02*
Division of Drug Risk Evaluation, HFD-430

FROM: Parivash Nourjah, Ph.D., Epidemiologist *PN 8/15/02*
Division of Drug Risk Evaluation, HFD-430
Mary E. Willy, Ph.D., M.P.H., Epidemiologist *Mary Willy 8/15/02*
Division of Drug Risk Evaluation, HFD-430

**SUBJECT: Drug: Epidemiolemy of Acetaminophen-related overdose
Topic: Hepatotoxicity
PID#: D010092**

I. EXECUTIVE SUMMARY

This memorandum is prepared in response to a request from the Division of Over-the Counter Drugs to study acetaminophen-related adverse outcomes in available national databases.

In summary, an analysis of three national surveys and national mortality data have provided the following APAP-related overdose findings:

Emergency Departments Surveys

- During 1993-1999, on average, 56,680 ED visits were made annually for APAP-related overdoses. APAP-related overdoses comprised seven percent of ED visits for all overdoses with drugs, medicinal substances and biologics.
- Among APAP-related overdoses visits made to EDs, 56% involved intentional overdoses, 23% involved unintentional overdose, and intentionality was unknown in the remainder.
- Among the unintentional overdoses evaluated in EDs, three-quarters were thought to be accidental ingestions and one-quarter were due to therapeutic misuse.
- In 43% of APAP-related overdose visits made to EDs, patients were admitted to a hospital or transferred to another facility.
- Alcohol intake was mentioned in about 10% of visits made to the ED related to APAP-related overdose.

- OTC APAP products were mentioned in 85% of APAP-related overdoses evaluated in EDs. Only 15% of overdoses involved prescription products containing APAP.

National Hospital Discharge Survey

- During 1990-1999, there were on average, 26,256 hospitalizations annually related to APAP overdoses. These comprised 11% of total hospital discharges related to overdoses with drugs, medicinal substances and biologics.
- Young children contribute to only 2% of APAP-related overdoses that are hospitalized and females contribute to nearly 70%.
- Alcohol related conditions were mentioned in about 19% of hospital discharges.
- In more than 74% of hospital discharges related to APAP overdoses, patients intentionally overdosed with APAP; patients unintentionally overdosed in 8% and intentionality is unknown in the remainder.
- Severe liver toxicity was reported in about 2% of APAP-related overdose hospitalizations, or approximately 548 discharges per year.

Mortality Data

- There are approximately 458 deaths related to APAP overdose each year, of which 100 are related to unintentional APAP overdose.
- The majority of patients who died from unintentional APAP-related overdose have liver disease listed in their death records.

The public health impact of APAP-related overdose in the US overall, and for unintentional APAP overdose in particular, is depicted in Figures 1 and 2 below.

II. BACKGROUND

Acetaminophen (APAP) is an antipyretic analgesic drug used widely around the world. It was first introduced in 1893 (1) and approved to be marketed as an over-the-counter product in the 1960s (1). Acetaminophen is now one of the most commonly used drugs in the United States (2-5). Except for the hepatotoxicity that has been associated with major overdoses, APAP has not been associated with any other major adverse drug reactions. APAP-induced hepatotoxicity may result in liver failure and deaths when expeditious treatment does not occur. APAP overdose is the leading cause of toxic drug ingestions in the United States (6) and is reported to contribute to 20% of all acute liver failures diagnosed in a multicenter acute liver failure study in the United States (7). Most APAP overdoses are the result of suicide or parasuicide (suicidal gesture) (8). About 14-21% of overdoses are related to therapeutic misuse/abuse and are classified as unintentional (8-9). Taking more than the recommended dose to relieve pain, abuse of narcotic APAP containing products, inadvertently taking several different APAP-containing products simultaneously, and taking the wrong dose because of confusion about the dose due to variation in concentrations and formulation among APAP products are among the patterns observed in unintentional overdoses. The APAP toxic dose is variable but it is usually achieved with a single dose over 10g, which is far more than the 4.0 g daily recommended for therapeutic use (10-11). There are some cases of APAP hepatotoxicity in which the patient's APAP dose was in the

therapeutic range or was at a modestly high dose of acetaminophen. Chronic ethanol ingestion (12-14), malnutrition (15), and concomitant use of APAP with certain drugs (16) or in certain disease conditions (17) are among factors which are proposed to enhance the toxicity of acetaminophen at therapeutic or at minimally toxic doses.

In this report, we estimate the public health impact of hepatotoxicity in the U.S. by analyzing various national databases.

Methods:

We examined the pattern of APAP-related overdoses seen at emergency departments (EDs), among hospitalized patients and among deceased individuals in the United States. Mortality data and three national surveys were used for this analysis. Two of the three surveys obtained data from EDs; the National Hospital Ambulatory Care Survey (NHAMCS) and the National Electronic Injury Surveillance System (NEISS). The third survey, the National Hospital Discharge Survey (NHDS), was used to describe APAP-related overdoses that resulted in admission to a hospital. We also used the National Multiple Cause of Death file to describe APAP-related deaths. The variables examined are listed in the table below.

Table 1. Characteristics of Nationally Representative, Population-Based Surveys

Variables	NHAMCS ED	NEISS	NHDS	Mortality
Total visits	Yes	Yes, but underestimated	Yes	Total deaths
Setting	ED	ED	Inpatient (hospital discharge)	deaths
Age	No	Yes	Yes	Yes
Sex	No	Yes	Yes	Yes
Intentionality Specified?	No	Yes	Yes (Proxy by codes)	Yes (Proxy by codes)
Ethanol Use Described?	No	Yes	Yes (Proxy by codes)	Yes (Proxy by codes)
Disposition	No	Yes	Yes	No
OTC APAP Distinguished?	No	Yes	No	No
Acute liver failure	No	No	Yes	Yes
Other liver problems	No	No	No	Yes

Emergency Department Evaluation of APAP-Related Overdoses:

Since both NEISS and NHAMCS collect data on ED visits, we used both databases to address different issues related to APAP overdoses. NHAMCS is not an appropriate database for studying intentionality because the definitions of intentionality of injury are inconsistent across different survey cycles and the sample size for the recent three survey years was not sufficient to provide a reliable estimate of intentionality. However, we were able to use NEISS to provide

insight about intentionality. Unlike NHAMCS, NEISS has sufficient sample size to characterize the intentionality of the APAP-related episode. We did not use NEISS to estimate the total number of APAP-related overdoses evaluated in EDs because the comment field that we used to identify APAP-related visits was limited to the drug product names listed in Appendix A. We do not believe this list includes all APAP products and, additionally, there are likely to be missed APAP cases because of misspelled product names. For these reasons, we used NHAMCS to provide an estimate for annual visits made to EDs for APAP-related overdoses (1993-1999), and we used NEISS to characterize the APAP-related overdoses with respect to demography, dispositions, and intentionality.

Survey Descriptions

The Centers for Disease Control and Prevention, National Center for Health Statistics (NCHS) conducts the National Hospital Ambulatory Medical Care Survey (NHAMCS) on an annual basis. One of the components of NHAMCS is a survey of ambulatory care services in hospital EDs. It is a probability sampling of visits made to EDs of non-institutional general and short-stay hospitals, exclusive of Federal, military, and Veterans Administration hospitals, located in the 50 States and the District of Columbia. Within selected hospitals, hospital staff are instructed to complete patient record forms for a systematic random sample of patient visits during a randomly assigned 4-week reporting period. Data are obtained on demographic characteristics of patients, expected source(s) of payment, patients' complaints, physicians' diagnoses, diagnostic/screening services, procedures, medication therapy, disposition, types of health care professionals seen, causes of injury (where applicable), and certain characteristics of the hospital, such as type of ownership. All listed diagnoses (up to 3) and all listed procedures (up to 4) are presented according to their code number in the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). In this survey the causes of injury are coded based on external causes of injury and overdose (E-CODE) of the international classification of diseases. Public use files of NHAMCS data were obtained by accessing the following Internet site: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHAMCS/.

The Consumer Product Safety Commission's (CPSC) National Electronic Injury Surveillance System All Injury Program (NEISS-AIP or NEISS), collects data on consumer product-related injuries treated in EDs. Annually a sample of 66 hospitals is selected to report injury-related information of all consumer product-related injuries treated at these hospitals. Data obtained include demographic characteristics of patients, product(s) involved, intentionality, diagnosis, body part affected, ER disposition, incident locale, fire involvement, and work related injuries. In this survey the cause of injury and the diagnosis are coded by definitions developed by CPSC. Our analyses used the specific product name data fields to distinguish prescription and OTC acetaminophen products (Appendix A). CPSC has collected data on drug overdoses in children under 6 years since the inception of its surveillance system in 1973. Starting in July 2000, data on drug injuries for individuals 6 years of age or older were collected as part of NEISS-AIP. The NEISS-AIP data used in our analyses were from special CD-ROM files made available by the CPSC solely to Federal government agencies. These files contain hospital identifiers and specific product names that are not releasable to the public.

APAP-Related Overdose Hospitalizations:

The National Hospital Discharge Survey (NHDS) is a national probability survey conducted annually to characterize inpatients discharged from non-Federal short-stay hospitals in the United States. Only hospitals with an average length of stay of fewer than 30 days for all patients, general hospitals, or children's general hospitals are included in the survey. Federal, military, and Department of Veteran's Administration hospitals, as well as hospital units of institutions (such as prison hospitals), and hospitals with fewer than six beds staffed for patient use, are excluded. Estimates are provided of demographic characteristics of patients discharged, geographic region of hospitals, conditions diagnosed, and surgical and nonsurgical procedures performed. Measurements of hospital use include number and rate of discharges and days of care, and the average length of stay. Estimates of first-listed diagnoses, days of care, all-listed diagnoses (up to 7), and all-listed procedures (up to 4) are presented according to their code number in the International Classification of Diseases, 9th Revision. In this survey, the diagnostic fields may include symptoms and illness codes as well as external cause of injury codes (e.g., external cause of injury due to accidental overdose with acetaminophen). All NHDS analyses were conducted on public use data files available either on CD-ROM (years 1990 – 1999) or the CDC Internet site: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Datasets/NHDS/.

APAP-Related Overdose Deaths:

The National Multiple Cause of Death file is a database that was developed and maintained through a collaboration between the NCHS and states that provide access to statistical information from death certificates. Medical information on the death certificate is coded using World Health Organization rules specified in the International Classification of Diseases (ICD). This file includes demographic and geographic information, and the underlying cause-of-death along with up to 20 contributing causes-of-death.

Definition of terms

NHAMCS-ED

- APAP-related visit
Any encounter which included the following codes: poisoning by aromatic analgesics, not elsewhere classified (965.4) or external cause of injury due to accidental poisoning by aromatic analgesics, not elsewhere classified (E850.4) were considered an APAP-related overdose visit. The aromatic analgesics included in these two codes were Paracetamol, Acetanilide and Phenacetin. The last two medications are no longer marketed in the United States, therefore these codes were considered to represent Paracetamol.

NEISS

- APAP-related visit
Any visit in which use of an APAP product [i.e., either prescription or over-the-counter (OTC)] was mentioned in the comment field and the cause of injury was defined as "poisoning".

- **Intentionality**
We used comment fields in the NEISS database to assign the intentionality of APAP poisoning. Our justification and method of coding is as follows: Overdosing from APAP can be intentional or unintentional with respect to injury. If the NEISS record mentioned “suicide”, it was categorized under intentionality as a *suicide*. If the word “suicide” or “hurting oneself” was not mentioned in the record, but there was a strong indication that the APAP overdose occurred intentionally (without therapeutic intent), the intent of APAP overdose was classified as *parasuicide*. For example, if the record mentioned the patient took APAP and had a relationship problem, or anger, the intentionality was categorized as *parasuicide*. Unintentional overdoses include ingestion, for example, when young children ingest drugs they are not supposed to. The intentionality of APAP-related overdoses for any child less than 6 years old was coded as *accidental ingestion*, unless stated otherwise. Another type of unintentional overdose is *therapeutic misuse*, which occurs when patients experience an APAP overdose as they are trying to reduce their symptoms, or when they are confused between drugs names or packages, or when they simultaneously use different APAP products (over-the counter products and prescription products). If cases could not be clearly classified as intentional (suicides or parasuicide), or unintentional (accidental ingestion or therapeutic misuse), the intentionality was classified as *unknown*. (See Appendix B)
- **Alcohol use**
Any use of ethanol or alcoholic beverages mentioned in the comment fields was taken to indicate pertinent exposure to alcohol.
- **Over-the-counter/prescription products**
APAP products were classified as either prescription or non-prescription/over-the-counter (OTC) depending on the brand name of the product.

NHDS

- APAP-related hospitalization - same codes were used as for NHAMCS-ED.
- Other poisoning by drugs, medicinal substances, and biologicals

Any poisonings due to medications other than APAP were defined by the injury and poisoning codes (960.0-965.3, 965.5-979.9) or external cause of injury (E850.0 – E850.3, E850.5-E858.9)
- **Intentionality**

The NHDS does not collect information on intentionality. Intentionality for APAP-related hospitalizations was classified using the following diagnostic codes (see Appendix B):
 1. Intentional
 - Any record with an external cause of injury listed as suicide or self-inflicted injury (E950-E959)] or

- Simultaneous poisoning with APAP and other medicinal and biologic substances (assumed to be presumptive suicides or parasuicides) were used as a surrogate for intentional overdosing.

2. Depressive disorders

- Any record with ICD-9 codes of 309.0-309.1(brief or prolonged depressive reactions), 311 (depressive disorder, not elsewhere classified), 301.12 (chronic depressive personality disorder), 301.13 (cyclothymic disorder), 300.4 (neurotic depression), 298.0 (psychogenic depressive psychosis), 296.2 (major depressive disorder, single), 296.3 (major depressive disorder, recurrent episode), 296.5 (bipolar affective disorder, manic), 296.6 (bipolar affective disorder, mixed), 296.8 (manic-depressive psychosis, other and unspecified), 308.0 (acute reaction to major stress, predominant disturbance of emotion), or 313.1 (disturbance of emotions specific to childhood and adolescence, with misery and unhappiness). Since depressive disorder is a risk factor for suicide and at the same time, people with chronic pain may be more prone to depression, we examined this disorder separately. These records were specifically excluded from the unintentional overdose category but were included under intentional or unknown as appropriate.

3. Unintentional overdose is defined as

- Any records with the code (E850.4) without any indication of intentional overdosing and/or depressive disorders.

4. "Unknown" intentionality is defined

- The remaining records which did not meet the above definitions.

- Alcohol-related conditions

- Any record that listed a toxic effect of alcohol (980.0), alcohol dependence syndrome (303), alcohol abuse (305.0), accidental poisoning by alcohol, not elsewhere classified (E860.0-E860.1), and alcoholic psychoses (291) was considered to be related to alcohol.

- Acute liver toxicity

We used ICD9-CM codes to define acute liver toxicity and its severity. The classification of liver toxicity was hierarchical and the severity was defined as follows:

- Any encounter that listed the diagnostic codes hepatorenal syndrome (572.4), hepatic coma/hepatic encephalopathy (572.2), acute or subacute liver necrosis/acute hepatic failure (570), liver transplant (V42.7), complications of liver transplanted organ (996.82), or any encounter that listed liver transplant as a procedure code (50.5) was considered a **severe/life threatening case**.
- Any encounter that did not meet criteria for severe/life-threatening and which listed jaundice (782.4), coagulopathy (286.9), coagulation defect due to liver disease (286.7), or biliuria (791.4) was considered a **moderately severe case**.

- Any encounter which was not otherwise classified as severe/life-threatening or moderately severe and which listed transaminasemia (790.4), or hepatitis, noninfectious toxic (573.3) was considered a **mild to moderate case**.
 - Any encounter which was not otherwise classified as severe/life-threatening, moderately severe or mild-moderate and which listed unspecified liver disorder (573.9) was considered an unknown or **unspecified case**.
- Liver diseases

The classification of liver disease was hierarchical and defined as follows:

 1. Acute Liver Toxicity
 2. Chronic alcoholic liver disease

Any record which was not otherwise classified as acute liver toxicity and which listed a liver problem related to alcohol was considered alcoholic liver disease (571.0-571.3).
 3. Chronic non-alcoholic liver disease

Any record which was not otherwise classified as acute liver toxicity or alcoholic liver disease and which was listed as chronic liver disease and cirrhosis “without mention of alcohol” (571.4-571.9).
 4. Other liver disease

Any record which was not otherwise classified as acute liver toxicity, alcoholic liver disease, or chronic liver disease, and which listed liver abscess and sequelae of chronic liver disease except for hepatic coma, hepatorenal syndrome, and portal hypertension (572.0-572.1, 572.3, 572.8), or other disorder of liver (573.0-573.2, 573.4-573.8) was considered other liver problem.
 5. No liver problem

Any record that did not list any liver conditions as defined above was considered as no liver problem.

Mortality Data

- APAP-related deaths

Any death record which included the following codes: poisoning by aromatic analgesics, not elsewhere classified (965.4) or external cause of injury due to accidental poisoning by aromatic analgesics, not elsewhere classified (E850.2) were considered an APAP-related poisoning visit. The aromatic analgesics included in these two codes were Paracetamol, Acetanilide and Phenacetin. The last two medications are no longer marketed in the United States, therefore, these codes were considered to represent Paracetamol.
- Other overdose by drugs, medicinal substances, and biologicals
 - Any poisonings due to medications other than APAP were defined by the injury and poisoning codes of : 960.0-965.3 and 965.5-979.9 or external cause of injury (E850.0 – E850.1, E850.3-E858.9)
- Intentionality

The mortality file does not collect information on intentionality. Intentionality of APAP-related deaths was defined in the same way as for NHDS data (see above and Appendix B):

1. Intentional- see above for NHDS

2. Depressive disorders

Any record with ICD-9 codes of 309.0-309.1 (brief or prolonged depressive reactions), 311 (depressive disorder, not elsewhere classified), 301.1 (affective personality disorder), 300.4 (neurotic depression), 298.0 (psychogenic depressive psychosis), 296.1 (Manic-depressive, depressive type), 296.3-296.6 (Manic-depressive psychosis: currently depressive type, mixed type, or unspecified type), 308.0 (acute reaction to major stress with depressive symptoms), or 313.1 (disturbance of emotions specific to childhood and adolescence, with misery and unhappiness). Since depressive disorder is a risk factor for suicide and at the same time, people with chronic pain may be more prone to depression, we examined this disorder separately. These records were specifically excluded from the unintentional overdose category but were included under intentional or unknown as appropriate.

3. Unintentional overdose- similar to NHDS definition except we used E805.2 rather than E805.4

4. "Unknown" intentionality -see above for NHDS

- Alcohol-related conditions:

Any record that listed toxic effect of alcohol (980.0), alcohol dependence syndrome (303), alcohol abuse (305.0), accidental poisoning by alcohol, not elsewhere classified (E860.0-E860.1), and alcoholic psychoses (291.0-291.9) was considered to be related to alcohol.

- Acute Liver Toxicity

The classification of liver toxicity was hierarchical and severity was defined as follows:

1. Any record that listed the diagnostic code hepatorenal syndrome (572.4), hepatic coma/hepatic encephalopathy (572.2), acute or subacute liver necrosis/acute hepatic failure (570), or liver transplant (V42.7) was considered a **severe/life threatening case**.

For mild to moderate, moderately severe, and unspecified liver toxicity see definitions listed under NHDS.

- Liver diseases: same categories as for NHDS.

Method of Analysis

All the surveys analyzed in this report were based on a sample of visits made to EDs (NEISS and NHAMCS-ED) or from hospital discharges (NHDS). National estimates of all ED visits and

hospital discharge encounters that occurred in the United States were obtained by giving each record a corresponding weighting factor provided in the databases.

The estimates of APAP-related visits from NHAMCS were based on weighted data for 96 APAP-related visits collected during 1993-1999 surveys. Data were weighted by the inverse of the probability of selection divided by 7 (the number of years analyzed) to provide an average annualized estimate of the national number of APAP-related overdose visits during the years 1993-1999.

The NEISS data were based on 340 APAP-related overdose visits made between January 1, 2001 to June 30, 2001. Each sample weight was multiplied by 2 in order to annualize estimates for the national population. We assumed there was no seasonality to APAP overdose.

The NHDS data was based on a sample of 2,232 APAP-related overdose hospital discharges during the years of 1990-1999. Each record was multiplied by its corresponding sample weight, and then divided by 10 in order to estimate the average annual hospital discharges.

The multiple cause of death file includes all death certificate data in the U.S. To get the average annual number of APAP-related overdose deaths during 1996-1998, each record was multiplied by a factor of 1/3.

Since NHAMCS, NEISS, and NHDS are sample surveys, the estimates are subject to sampling variability that can occur by chance. The reliability of each estimate is related to the sampling variability. It should be noted that estimates based on less than 30 counts are considered unreliable regardless of the magnitude of sampling variability. In this report, data are not presented in tables when the sample size is less than 30; however, we report the qualitative findings in the text.

III. REVIEW OF NATIONAL DATABASES

Emergency Departments

The NHAMCS database was used only to estimate the annual ED visits related to APAP overdoses for the years 1993-1999 and the contribution of APAP-related overdoses to overall visits associated with overdose by drugs, medicinal substances, and biologics. The NEISS database was used to describe the characteristics of APAP-related visits to EDs.

Based on NHAMCS, during 1993-1999 an average of 56,680 ED visits were made annually for APAP-related overdose. The APAP-related visits comprised about eight percent of ED visits related to all medicinal and biologic substance overdoses.

In Table 2, the description of APAP-related overdose visits made to EDs in 2001 based on NEISS is displayed. In about 17% of such visits, the patient's age was 5 years or younger. The

majority (65%) of APAP-related visits were 17 to 64 year olds. The percentage of visits made by females was higher than for males (63% vs. 37%).

Twenty-three percent of APAP-related ED visits were unintentional; 17% were due to accidental ingestions and approximately 6% were due to therapeutic misuse. (Note: The estimate for therapeutic misuse is approximate since it is based on less than 30 cases.) The majority of the APAP-related visits among patients less than 6 years of age were due to accidental ingestion. (Note: The preponderance of this type of visit in children could be due to our coding procedure which classified APAP-related overdoses in children less than 6 years of age as unintentional ingestions unless there was evidence of therapeutic misuse of the medication.) In 56% of APAP-related ED visits the overdose was intentional, either suicide attempt (44%) or parasuicide (12%). In 20% the intentionality could not be assessed (Table 2).

In about 55% of ED visits, the patients were released home. In as many as 43% of visits, the patients were admitted to the hospital (either to the same hospital or other hospital, including long/short term facilities), and 2% were held for further observation. None of these patients died in the surveyed hospitals. (A few deaths were observed in NHAMCS-ED, suggesting that death occurs rarely in Emergency Departments.)

Further examination of intentionality and hospital disposition in NEISS showed that intentional overdose cases tend to be older, female, and be transferred to the hospital than unintentional overdoses (data not shown).

According to NEISS, only 15% of APAP-related visits involved a prescription product containing APAP. In about 85% of these visits, the patients used exclusively over-the-counter (OTC) products. Over-the-counter products were more frequently reported among unintentional APAP-related overdoses than intentional APAP-related overdoses. However, when comparing OTC versus Rx product use and intent it is important to remember that the root cause for unintentional overdoses among children (accidental ingestion) generally occurs with OTC products and thus the overall percentage of OTC products used among unintentional overdoses is skewed. When we compared unintentional overdoses by therapeutic misuse to intentional overdoses we found Rx products were more common in the unintentional group, although the numbers were too small to make a definite conclusion.

Hospital Discharges

During 1990-1999, there were on average, 26,256, hospitalizations annually related to APAP overdoses. These comprised 11% of total hospital discharges related to overdoses with drugs, medicinal substances, and biologics (Table 3). Although there was no significant change in the percent of hospitalizations due to overdose by all drugs and biologics between the periods of 1990-1994 and 1995-1999, there was a slight increase in percent of APAP-related overdoses during the period 1995-1999 compared to the 1990-1994 period (data not shown).

In about 73% of APAP-related overdose hospitalizations, the patient ages were between 17-64 years, and in 21%, the patients were between 6 and 17 years. A small percentage of APAP-

related overdose hospitalizations were among individuals younger than 6 years or older than 65 years. The percentage of females hospitalized was higher than for males (69% vs. 31%). A review of the other diagnostic codes associated with APAP-related overdose hospitalizations in the NHDS suggest that 74% of the hospitalized cases were intentional. Suicide was coded in 60% of discharges; overdose due to APAP with other medicinals (i.e., parasuicide) was listed in about 41%. About 8% of hospitalizations had a listing for unintentional APAP overdose without a listing for either suicide, overdose with other drugs, medicinal substances and biologics, or depressive disorders. The intentionality of the remaining encounters was considered unknown.

Alcohol-related conditions were listed in 19% of all APAP-related overdose hospital discharges. In APAP-related encounters regardless of their intentionality, the level of alcohol-related conditions was quite high in comparison to the level of alcohol-related conditions among all other discharges in the database (i.e. for any other conditions) (3%).

Few (5%) of the hospital encounters had evidence of hepatotoxicity. Of these, about 42% were described as severe or life threatening liver toxicity (that is, about 2% of all APAP-related hospitalizations or about 548 hospitalizations per year).

In about 73% of all APAP-related overdose hospital discharges, the patients were treated and discharged to home. In about 11% of encounters, the patients were transferred to short-term facilities, and in 3% of encounters, patients were transferred to long-term facilities. Patients died in less than 1% of APAP-related overdose hospital discharges (approximately 200 deaths per year)

In Table 4, we display the percent of encounters for some selected variables by intentionality. Compared to patients with intentional overdoses, patients who were hospitalized for unintentional overdoses were equally distributed by genders, were more likely to have acute liver toxicity and more likely to be discharged to home than intentional overdoses. Note, due to the small size of some categories, this interpretation should be taken with caution.

Mortality files:

During 1996-1998, a total of 1375 deaths identified in which APAP overdosing was either the underlying cause of death or was a contributing cause of death (See Table 5). One thousand ten records had mentioned either suicide or intentional overdose, 7 deaths had included a depressive disorder (i.e., without any indication of suicide or parasuicide), 300 deaths were listed as an APAP-related unintentional overdose, and in 58 APAP related overdoses, the intentionality could not be defined. In summary, during 1996-1998, the average annual deaths from APAP-related overdose is about 458 of which 22% can be attributed to unintentional overdose.

About 58% of APAP-related deaths occurred among females. About 14% of the deaths occurred among persons who were 65 years or older. There were six deaths in which the deceased persons were less than 6 years of age. One died from unintentional overdose and 3 died from intentional overdose. Although these three children had "accidental poisoning by acetaminophen" listed as

underlying cause-of-death, we classified them as intentional because they had APAP overdose along with other drug overdoses (see Page 9). Note: among the 1010 intentional overdose cases, there are a total of 49 deaths related to “accidental poisoning by acetaminophen” but because of our definition, they are classified here as intentional overdose.

Compared to intentional overdose cases, unintentional overdose cases had a higher percentage of 64 or older aged persons (23% vs. 11%)

About 6% of all APAP- related overdose deaths had alcohol-related conditions. The percentage of cases with alcohol related conditions was higher for intentional than unintentional overdose cases (7.0% vs. 3.0%.) About 13% of APAP-related deaths were reported to have acute liver toxicity. Acute liver toxicity was higher among unintentional APAP-related deaths (28%) than intentional deaths (8%).

Overall, fatal unintentional APAP-related overdoses had a relatively higher proportion of any type of liver disease including chronic alcoholic, chronic non-alcoholic and other liver disorders. Further analysis of the "other liver diseases" found that almost all cases had a condition recorded as “other sequelae of chronic disease.”

IV. DISCUSSION

Acetaminophen is available at any supermarket or convenience store; it is manufactured as a single ingredient or in combination with other OTC or prescription drugs; and it is manufactured in various formulations and concentrations. These variations in manufacturing and packaging as well as the ease of access have created opportunities for misuse or abuse of this generally safe and effective medication. In the 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), there were 108,102 APAP-related calls representing 10% of 1,020,598 exposures reported with all pharmaceutical substances (18). Combining this information with our findings, we summarize the public health impact of APAP overdose cases in Table 6 and Figure 1 below. Note, in this figure, each estimate is derived from a source which is independent from other sources. For example, all 458 deaths reported in death files might not have occurred in the hospital. Deaths may have occurred at home, during transfer to the emergency department or at emergency departments.

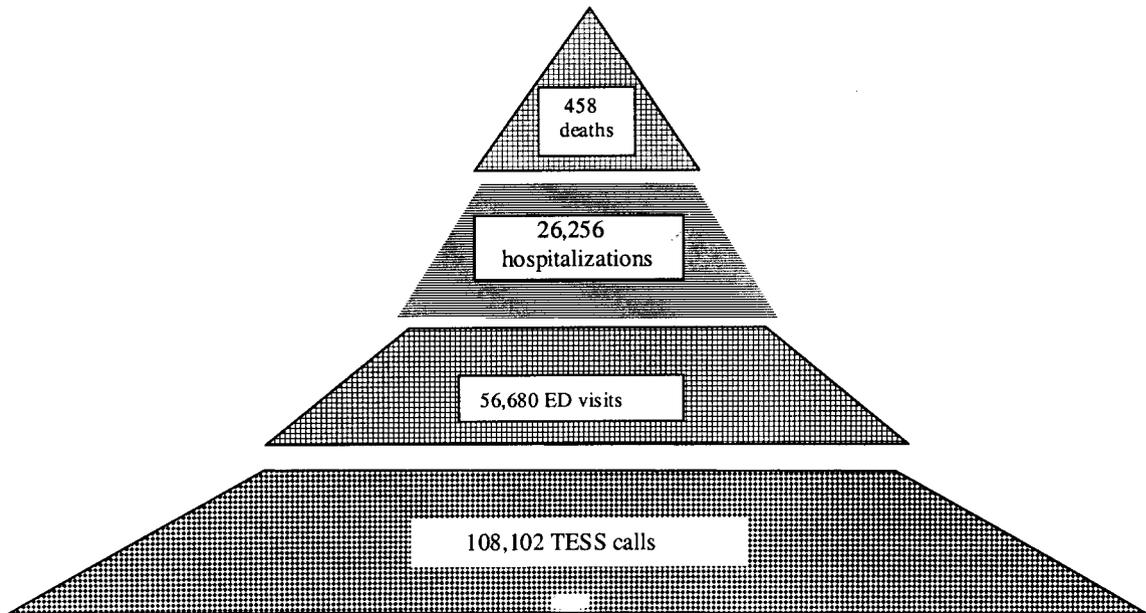


Figure 1. The number of APAP-related overdose presentations to the TESS (1999), ED (averaged for the years 1993-1999), NHDS (averaged for the years 1990-1999), and mortality data (averaged for the years 1996-1998). These estimates are independent.

The majority of APAP-related overdoses are deliberate self-harm episodes. Unintentional overdoses comprised about 8% to 23% of APAP related cases depending on the data source examined. In Figure 2, we depict the public health burden of unintentional APAP overdoses in the US.

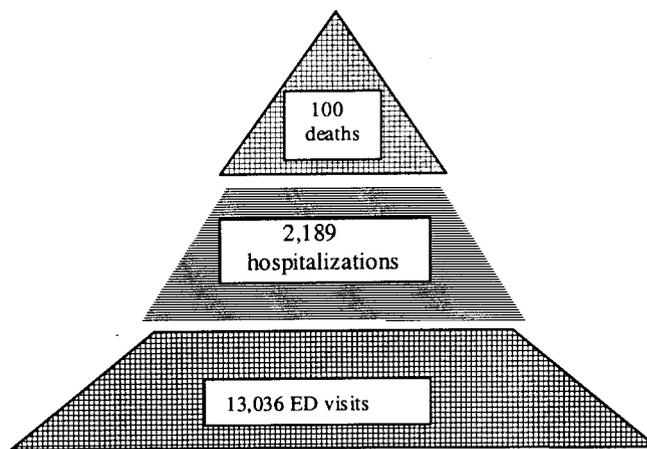


Figure 2. The number of APAP-related unintentional presentations to the ED (averaged for the years 1993-1999), NHDS (averaged for the years 1990-1999), and mortality data (averaged for the years 1996-1998). These estimates are independent.

Unintentional overdose due to therapeutic misuse has been reported in the literature to contribute to 14%-21% of all APAP-related overdose hospitalizations in urban county hospitals (8-9). These cases are reported to have lower APAP doses, to be severe and more likely fatal compared to intentional cases (8-9). The potential for delay in treatment of unintentional overdose cases is proposed to be the reason for the high morbidity and mortality (19). In this report, we could not make any meaningful comparisons of mortality and morbidity between unintentional and intentional APAP overdose cases because either the data source did not collect information on outcome of the overdose (e.g., NEISS) or the data were too scarce to make an appropriate comparison (e.g., NHDS or NHAMCS).

The death certificate data provided information on associated liver diseases. Intentional fatal APAP overdose cases were less likely to have concomitant acute liver disease than unintentional cases. This finding is not surprising since intentional APAP-related overdoses were often associated with ingestion of other medicinal substances or chemicals so the injury could have been the result of other agents (about 85% of intentional fatal APAP overdoses are associated with other drugs, medicinal substances and biologics, data not shown). Note, by definition unintentional overdose could only have been due to APAP overdose (i.e., without any other medicinal products). Overall, fatal unintentional APAP-related overdoses had a higher proportion of non-alcoholic and alcoholic liver disease, and "other sequelae of chronic liver disease." The higher percent of liver disease in unintentional APAP-related overdoses compared to intentional overdoses (75% vs. 16%) remains significant even after adjusting for age and sex.

In this report we completed secondary analyses on several databases to address the public health impact of APAP overdose. We were limited by the definitions used and data gathered in these databases. The data collected in these databases usually cover the conditions that were diagnosed at the time of patient presentation at the setting and therefore, do not reflect the true prevalence

of the conditions. Also, some conditions such as suicide or alcoholic liver disease may have had intentionality listed as unintentional overdose or as “chronic liver disease” respectively to minimize the social stigma associated with these conditions. The observed difference in liver conditions between intentional and unintentional overdose could be due to a detection bias of the medical examiner – in unintentional cases, the medical examiner may look for the presence of underlying disease that may explain the cause of death. We were also limited by using a series of codes that may not represent the true prevalence of these conditions.

REFERENCES

1. Makin A.J., Williams R. (1997): Acetaminophen-induced Hepatotoxicity: Predisposing Factors and Treatments. *Advances in Internal Medicine* 42:453-483
2. Cherry D.K., Burt C., and Woodwell D. (2001): National Ambulatory Medical Care Survey: 1999 Summary. *Advance Data* from Vital and Health Statistics No. 322. Hyattsville, Maryland.
3. Ly N., McCaig L., and Burt C. (2001): National Hospital Ambulatory Medical Care Survey: 1999 Outpatient Department Summary. *Advance Data* Vital and Health Statistics No. 321. Hyattsville, Maryland.
4. McCaig L., and Burt C. (2001): National Hospital Ambulatory Medical Care Survey: 1999 Emergency Department Summary *Advance Data* Vital and Health Statistics No. 320. Hyattsville, Maryland.
5. Kaufman D.W., Kelly J.P., Rosenberg L., Anderson T., Mitchell A. (2000): Recent Patterns of Medication Use in the Ambulatory Adult Population of the United States, The Slone Survey. *JAMA* 287, 337-344.
6. Litovitz T.L., Klein-Schwartz W., White S., Cobaugh D.G., Youniss J., Drab A. (1999): 1998 Annual Report of the American Association of the Poison Control Toxic Exposure Surveillance System. *Am J Emerg Med*, 17:435-487.
7. Schiodt F.V., Atillasoy E. Shakil A.O. Schiff E.R., Caldwell C., Kowdley K.V., Stribling R., Crippin J.S., Flamm S., Somberg K.A., Rosen H., McCashland T.M., Hay J.E., Lee W.M, and the Acute Liver Failure Study Group (1999): Etiology and Outcome for 295 patients with Acute Liver Failure in the United States. *Liver Transplantation and Surgery*, 5; 29-34.
8. Schiodt F.V., Rochling A.F., Casey D.L., and Lee W.M. (1997): Acetaminophen Toxicity in an Urban County Hospital. *N Engl J Med* 337:1112-7
9. Gyamlani G.G. and Parikh C.R. (2002): Acetaminophen Toxicity: Suicidal vs. Accidental. *Critical Care* 6:155-159
10. Tanaka E., Yamazaki K. and Misawa S. (2000): Update: The Clinical Importance of Acetaminophen Hepatotoxicity in Non-alcoholic and Alcoholic Subjects *Journal of Clinical Pharmacy and Therapeutics* 25, 325-332
11. Johnston S.C. and Pelletier, L.L. (1997): Enhanced Hepatotoxicity of Acetaminophen in Alcoholic Patient: Two case Reports and a Review of the Literature *Medicine* 70:1855-91
12. Draganov P., Durrence H., Cox C., Reuben A. (2000): Alcohol-acetaminophen Syndrome. Even Moderate Social Drinkers Are at Risk. *Postgraduate Medicine*, 107: 189-195.
13. Zimmerman H.J. and Maddrey W.C. (1995): Acetaminophen (Paracetamol) Hepatotoxicity with Regular Intake of Alcohol : Analysis of Instances of Therapeutic Misadventure. *Hepatology* 22: 767-773.
14. Seeff L.B., Cuccherini B.A., Zimmerman H.J., Alder E., Benjamin S.B. (1986): Actaminophen Hepatotoxicity in Alcoholics: A Therapeutic Misadventure. *Ann Intern Med* 104 (3): 399-404
15. Whitcomb D.C., Block G.D. (1994): Association of Acetaminophen Hepatotoxicity with Fasting and Ethanol Use. *JAMA* 272: 1845-1850.
16. Pirotte J.H.: Apparent Potentiation by Phenobarbital of Hepatotoxicity from Small Doses of Acetaminophen (1984): *Ann Intern Med* 101:403
17. Johnson K., Tolman K.G. (1997): Chronic Liver Disease and Acetaminophen *Ann Intern Med* 87: 302-304

18. Litovitz T.L., Klein-Schwartz W., White S., Cobaugh D.J., Youniss J., Drab A., Benson B.E. (2000): 1999 Annual Report of the American Association of Poison Control Center Toxic Exposure Surveillance System. *Am J Emerg Med* 18(5);517-574
19. McClain C.J., Holtzman J., Allen J., Kromhout J., Shedlofsky S. (1988): Clinical Features of Acetaminophen Toxicity. *J Clin Gastroenterol* 10: 76-80

Parivash Nourjah, Ph.D.
Epidemiologist

Mary Willy, Ph.D.
Epidemiologist

Concur:

Julie Beitz, M.D.
Director

Table 2. The Characteristic of APAP-Related Overdose Visits Made to EDs (NEISS) –2001

Variables	Weighted Estimate	Percent	Sample size
Total	40,997	100	340
Age group			
<6 years	7,132	17.4	75
6-16 years	6,539	15.9	65
17-64 years	26,578	64.8	191
>65 years	**	**	**
Gender			
Female	25,822	63.0	221
Male	15,174	37.0	119
Intentionality category			
Unintentional			
Accidental ingestion	7,066	17.2	72
Therapeutic misuse	**	6.1**	**
Intentional			
Suicide	18,150	44.3	137
Parasuicide (OD with anger, depression, etc.)	4,998	12.2	39
Unknown	8,266	20.2	69
Disposition			
Treated and released, or examined and Released without treatment	22,499	54.8	199
Treated and transferred to another hospital	3,960	9.6	31
Treated and admitted for hospitalization (within the same hospital)	13,610	33.2	104
Held for observation	**	**	**
Alcohol use mentioned			
Yes	**	**	**
No	36,828	89.8	317
Over the counter APAP products mentioned			
Yes	34,968	85.3	291
No	6,028	14.7	49

**Sample size less than 30 is not displayed

Table 3. Distribution of Selected Variables Among APAP-Related Overdose Hospitalizations: NHDS, 1990-1999

	Estimated Number ⁺	Percent	Sample Size
Total	26,256	100%	2,232
Age Group			
<6	518	2.0	42
6-16	5,636	21.5	535
17-64	19,188	73.0	1,585
65+	915	3.5	70
Sex			
Male	8,174	31.1	677
Female	18,082	68.9	1,555
Suicide Coded			
Yes	15,641	59.6	1,271
No	10,615	40.4	961
Other Medicinal Poisoning (with APAP)			
Yes	10,810	41.2	841
No	15,446	58.8	1,391
Alcohol-Related Conditions			
Yes	4,903	18.7	370
No	21,353	81.3	1,862
Intentionality			
Suicide/other poisoning (Intentional)	19,514	74.3	1,587
Unintentional	2,189	8.3	137
Depressive disorders/Unknown	4,553	17.4	508
Acute Liver Toxicity			
Not mentioned	24,948	95.0	2,126
Unspecified	**	**	**
Mild-moderate	614	2.3	60
Moderately severe	**	**	**
Severe/life threatening	548	2.1	40
Discharge			
Routine/discharged home	19,051	72.6	1,550
Left against medical advice	835	3.2	84
Discharged/transferred to short-term facility	2,781	10.6	196
Discharged/transferred to long-term care institution	799	3.0	85
Alive, disposition not stated	2,242	8.5	273
Dead	**	**	**
Not stated or not reported	349	1.3	31

⁺ Data represents averaged yearly estimates for the period

** Data are not displayed because of small sample size (less than 30 counts)

Table 4. The Percent Distribution of Selected Variables by Intentionality: NHDS, 1990-1999

Selected variables	Intentional (N=1587)*	Unintentional (N=137)
Total	100% ⁺	100% ⁺
Age Group		
<6	1.0**	**
6-16	22.1	**
17-64	73.6	70.8
65+	3.3	**
Sex		
Male	30.4	49.5
Female	69.6	50.5
Alcohol-Related Conditions		
Yes	18.5	19.6**
No	81.5	81.4
Any Acute Liver Toxicity ***		
Yes	3.6	15.0**
No	96.4	85.0
Any Liver Disease		
Yes	4.4	**
No	95.6	84.1
Discharge		
Routine/discharged home	69.4	87.3
Left against medical advice	3.4	**
Discharged/transferred to short-term facility	12.2	**
Discharged/transferred to long-term care institution	3.0	**
Alive, disposition not stated	10.5	**
Dead	**	**
Not stated or not reported	**	**

*N is the actual sample size.

⁺ Averaged yearly estimates for intentional and unintentional is 19,514 and 2,189 respectively.

** Sample size is less than 30

*** Any indication of acute liver toxicity problems, including unknown/unspecified liver injury, was included as 'yes'.

Table 5. Distribution of APAP-Related Deaths by Sex, Age, Liver Conditions, and Intentionality, Multiple Cause of Deaths, 1996-1998, United States

Variables	All*		Intentional		Unintentional	
	counts	percent	counts	percent	counts	percent
Sex	1,375	100.0	1010	100.0	300	100.0
males	577	42.0	449	44.5	114	38.0
females	798	58.0	561	55.5	186	62.0
Age (years old)						
<6	6	0.4	3	0.3	1	0.3
6-16	16	1.2	11	1.1	4	1.3
17-64	1165	84.7	886	87.7	226	75.3
>64+	188	13.7	110	10.9	69	23.0
Alcohol-related conditions						
yes	82	6.0	71	7.0	9	3.0
no	1293	94.0	939	93.0	291	97.0
Acute liver Toxicity						
not mentioned	1200	87.3	934	92.5	216	72.0
unspecified	2	0.2	0	0.0	2	0.7
mild-moderate	8	0.5	3	0.3	4	1.3
moderately severe	5	0.4	2	0.2	3	1.0
severe/life threatening	160	11.6	71	7.0	75	25.0
Liver diseases						
acute liver toxicity	175	12.7	76	7.5	84	28.0
chronic alcoholic	36	2.6	10	1.0	25	8.3
chronic non-alcoholic	27	2.0	11	1.1	14	4.7
other	183	13.3	67	6.6	100	33.3
no liver disease	954	69.4	846	83.8	77	25.7

* Includes intentional, unintentional, and unknown intentionality.

Table 6. A Summary of Percent Distribution of APAP-Related Poisoning Visits by Selected Variable and Medical Setting

Variables	Emergency		NHDS 1990-1999 ⁺	Mortality 1996-1998 ⁺
	NHAMCS 1993-1999 ⁺	NEISS 2001 ⁺		
Total		100%	100%	100%
Age (years)				
<6		17.4	2.0	0.4
6-16		15.9	21.5	1.2
17-46		64.8	73.5	84.7
>65		**	3.5	13.7
Sex				
Male		37.1	31.1	42.0
Female		62.9	68.9	58.0
Intentionality				
Intentional		56.5	74.3	73.5
Unintentional		23.3	8.3	21.8
Unknown		20.2	17.4	4.7
Ethanol use/current alcohol-related conditions				
Yes		**	18.7	6.0
No		89.8	81.3	94.0
Disposition				
Treated and released home		54.8	72.6	
Treated and transferred to another hospital		9.6		
long term facility		NA	10.6	
short term facility		NA	3.0	NA
Treated and admitted for hospitalization		33.2		
Held for observation		**		
Death			**	
Unknown			1.3	
Other			11.7	
Acute Liver Toxicity		NA		
Not Mentioned			95.0	87.3
Unspecified Liver Diseases			**	0.2
Mild-Moderate			2.3	0.6
Moderately Severe			**	0.4
Severe/Life Threatening			2.1	11.6
OTC APAP products mentioned				
Yes		85.3	NA	NA
No		14.7		

+ Averaged yearly estimates for the period: NHAMCS: 56,680, NEISS: 40,997, NHDS: 26,256, and Mortality:458

** Sample size is less than 30

Appendix A. List of APAP Products Used to Ascertain APAP-Related Overdose Visits, NEISS

ACEPHEN
ACETAMINOPHEN
ACETAMINOPHEN AND HYDROCODONE BITARTRATE
ACETAMINOPHEN AND HYDROCODONE DITARTRATE
ACETAMINOPHEN AND OXYCODONE HCL
ACETAMINOPHEN SLOW RELEASE
ACETAMINOPHEN W/ PROPOXYPHENE HCL
ACETAMINOPHEN WITH PROPOXYPHENE HCL TAB
ACETAMINOPHEN- PROPOXYPHENE HCL TAB
ALGOSON TAB
ALLAY
ANEXSIA
ANEXSIA 7.5/650
APAMIDE TAB
APAP TAB
APAPAP W/ HYDROCODONE
BANCAP HC
BENYLIN
BUTORPHANOL TARTRATE-ACETAMINOPHEN
CO-GESIC
CO-GESIC FORTE
COPLEXEN LIQUID
DAMACET-P
DARVOCET
DARVOCET-N 100
DARVOCET-N 50
DATRIL W/ OXYCODONE
DIAP TAB
DOLENE AP-65
DRIXORAL NON DROWSY COLD AND FLU
DRIXORAL PLUS
DURAC SRT
DURADYNE DHC
EXTRA STRENGTH TYLENOL
FEVERALL
HY-PHEN
HYDROCET
HYDROCODINE BITARTRATE AND ACETAMINOPHEN
HYDROCODONE BITARATE AND ACETAMINOPHEN
HYDROCODONE BITARTRATE
HYDROCODONE BITARTRATE & ACETAMINOPHEN
HYDROCODONE BITARTRATE AND ACETAMINOPHEN
HYDROCODONE BITARTRATE AND ACETAMINPHEN
HYDROCODONE BITARTTATE AND ACETAMINOPHEN
INJECTAPAP
LORCET-HD
LORTAB
LULLAMIN DPS
METALID TAB
MJ #114 CRC
NALBUPHINE HCL W/ ACETAMINOPHEN

Appendix A, continued.

NAVANOL SR
NEBS
NEOPAP
NORACET
NORCET
NORCO
NYSACETOL TAB
OXYCET
OXYCODONE 2.5/APAP 500
OXYCODONE 5/APAP 500
OXYCODONE AND ACETAMINOPHEN
OXYCODONE AND ACETAMINPHEN
OXYCODONE HCL AND ACETAMINIPHEN
OXYCODONE HCL AND ACETAMINOPHEN
OXYCODONE HYDROCHLORIDE AND ACETAMINOPHEN
PENTAZOCINE HCL AND ACETAMINOPHEN
PERCOCET
PERCOCET-5
PRODUCT 5022 4AZ SYRUP
PROPACET 100
PROPAP-100
PROPOXYPHENE HCL
PROPOXYPHENE HCL AND ACETAMINOPHEN
PROPOXYPHENE HCL W/ APAP
PROPOXYPHENE HYDROCHLORIDE AND ACETAMINOPHEN TAB
PROPOXYPHENE HYDROCHLORIDE W/ ACETAMINOPHEN TAB
PROPOXYPHENE HYDROCHLORIDE W/ACETAMINOPHEN TAB
PROPOXYPHENE HYDROCHLORIDE-ACETAMINOPHEN-COMPARATIVE
STUDY-TAB
PROPOXYPHENE NAPSYLATE AND ACETAMINOPHEN
PROPOXYPHENE NAPSYLATE W/ ACETAMINOPHEN
PROPOXYPHENE/ ACETAMINOPHEN COMBINATION PROTOCOL CAP
QUADRIN
ROBAXACET
ROXICET
ROXICET 5/500
ROXILOX
ST. JOSEPH PEDIATRIC SYRUP
STRILAXIN TAB
TALACEN
TAVIST ALLERGY/SINUS/HEADACHE
TEMPRA SYRUP
TEPRIN TAB
TRALGON
TRAMADOL HYDROCHLORIDE/ACETAMINOPHEN
TRENDAR
TYCOLET
TYLENOL
TYLENOL SUPPOSITORIES
TYLENOL-500
TYLOX
TYLOX-325

Appendix A, continued

UNISOM DUAL RELIEF
VICODIN
VICODIN ES
VICODIN HP
WYGESIC
X-OTAG
X-OTAG PLUS TAB

Appendix B. Classification of Intentionality by Database

Terms	NEISS	NHDS/Mortality
<p>Intentional Suicide</p> <p>Parasuicide (presumptive suicidal intent)</p>	<p>'Suicide' mentioned</p> <p>'Anger', or 'relationship problem' mentioned</p>	<p>Codes for suicide or self-inflicted injury</p> <p>Codes for APAP and other drugs, medicinal, biological substances</p>
<p>Unintentional</p> <p>Accidental ingestions</p> <p>Therapeutic misuse</p>	<p>'Ingestion', or by age of child in absence of any indication of therapeutic 'misuse'</p> <p>Mentioned taking APAP for pain symptoms, or product confusion, or simultaneous use of different APAP-products with therapeutic intent</p>	<p>Code for unintentional overdose due to acetaminophen in absence of any code for depression and intentional overdose</p>
<p>Unknown/Depressive disorders</p>	<p>Not classified as intentional or unintentional</p>	<p>Not classified as intentional or unintentional</p>