

Response to Correspondence of September 15, 2003 (tracking 2465)

From: Curtis Rosebraugh, M.D., M.P.H
Division of OTC Drug Products
Deputy Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Docket No. 81N-0050

Respond to:

Paper copy to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.
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Response prepared by:

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Background:

Data from the Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Centers were analyzed to respond to the questions.

For more detailed information about the TESS database and definitions, please see the Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System available at <http://www.aapcc.org/poison1.htm>. or Watson WA, Litovitz TL, Rodgers GC, et al. 2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. American Journal of Emergency Medicine 2003; Vol 21, number 5:353-421.

Note: Unless otherwise noted, the following criteria were used to define the population.

1. Human poison exposures occurring in children ≤ 5 years of age.
2. Exposure route ingestion (with or without other routes).
3. The exposure involved one substance (cases with ingestion of multiple substances were excluded).
4. Cases were closed and an outcome was documented. Duplicate cases (reported by more than one poison center) were excluded.

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5. Cases were excluded that were ultimately determined not to be exposures and documented to be confirmed non-exposures.
6. Cases were managed at the site where the exposure occurred (a non-health care facility); the management site was most commonly the patient's residence.
7. Cases were not included if the poisoning exposure substance was ipecac.
8. From 1989 through 1999, ipecac administration was documented without information about whether administration was recommended by the poison control center. From January 2000 forward documentation of whether or not ipecac was recommended by the poison control center is available in TESS.

Over the 15 year period analyzed (1989-2003) the total number and percentage of pediatric cases that received ipecac has steadily declined since 1992 (Figure 1, Figure 2). The number of cases treated with ipecac each month is seasonal. More cases had ipecac administered in September, October, or November of each year from 1989 through 2001 when compared to other months.

Question 1. In what types of poisonings was ipecac used?

Response: During the 15 year interval, poison centers documented the administration of ipecac in 743,046 human exposures (all ages and treatment sites). In 338,586 cases (45.6%), the exposure involved the ingestion of a single substance by a child < 6 years of age who was managed at home. The pediatric cases managed at home make up the population reported to determine what poison exposures were most commonly involved in home ipecac administration, with the additional criteria listed in the note section on the first page of this document.

The AAPCC TESS has 66 major substance categories in Table 22a and Table 22b of the Annual Report. The vast majority of ipecac treatment (91.5%) occurred in 19 of the 66 major categories. To assess the frequency of ipecac administration over time, three intervals of five years each (1989 - 1993; 1994 - 1998; and 1999 - 2003) were created. The number and percentage of cases in each of the 19 categories that had ipecac administered consistently decreased over the evaluation time interval. (Table 1) Ipecac was most frequently administered to mushroom ingestions managed at home during the three time intervals, 68.66%, 53.19%, and 34.87%, respectively. Unknown mushrooms accounted for 99% of all ipecac administration after all mushroom ingestions.

Question 2. Who recommended the home use of ipecac?

Response: At the beginning of 2000, TESS data fields and definitions were modified to include information about treatments which were undertaken upon the recommendation of a poison control center. This allows differentiation of ipecac administered in response to a poison control center's recommendation from other administration. The term "recommended" refers to administration following a poison center recommendation; it is not a judgment of the appropriateness of ipecac use.

Since January 2000 the total number of pediatric exposures treated with ipecac has declined (Figure 3). The large number of cases with ipecac not recommended in January 2000 is likely due to delayed implementation of a major coding revision by some US poison centers. Ipecac administration by the caller (not recommended by a poison control center) remained fairly constant after February 2000, ranging from 200 to 273 cases per month for 2000 and 2001, declining to a range of 129 to 263 cases per month for 2002 and 2003. The majority of the decline was due to the decreased frequency that ipecac administration was recommended by poison control centers.

In November 2003, the American Academy of Pediatrics (AAP) released a policy statement on poison treatment in the home (Pediatrics 2003;112(5):1182). The statement reversed their long-standing recommendation that ipecac should be kept in the home. The AAP also recommended that ipecac should not routinely be used as a home treatment for pediatric poison exposures. The release of this policy coincides with a noticeable decrease in poison control center recommendation of ipecac administration (Figure 3, Figure 4).

Table 2 describes the number of cases and percentage of ipecac administration recommended by poison control centers since January 2000 for the 19 major categories most commonly receiving ipecac. In children managed at home following mushroom ingestions, more than 95% of ipecac administration was recommended by a poison control center.

Questions 3 and 4. What were the outcomes of these poisonings? How did the outcomes of poisonings that received ipecac and were managed at home compare to similar cases where ipecac was not recommended?

Response: The decision to recommend ipecac treatment at home is broadly based on a determination by the poison control center that a clinically significant exposure has occurred that does not need evaluation at a health care facility, and that ipecac may be effective in decreasing the exposure to a level that would minimize toxicity. For this reason, a comparison of cases that received ipecac home management to those that received no gastrointestinal decontamination would not be reasonable, even if the substances were similar, unless an adjustment for the dose implicated were possible.

One of the treatments documented in TESS is whether an emetic other than ipecac is used. This code is used for any procedure or substance administered as an emetic, whether or not it is effective or appropriate, including mechanical stimulation (gagging), mustard, eggs, salt water, peroxide, detergent solutions, and others. Other emetic treatment between 2000 and 2003 was initiated by the caller without being recommended by the poison control center in 87.6% of cases. The use of a dilute, mild hand dishwashing detergent solution has been evaluated as a method of inducing emesis for patients when ipecac is not readily available. As shown in Figure 5, the use of alternative emetics has steadily increased over the last 15 years.

The medical outcomes associated with ipecac cases and other emetics are compared in Table 3. Outcomes after ipecac administration are less severe and more likely to be followed-up by the poison control center than cases in which other emetic treatments were used. This may be secondary to greater efficacy of ipecac compared to other emetics, the lower frequency of adverse reactions to ipecac treatment, or differences

in the exposure toxicity. The number of adverse reactions to treatment is also listed in Table 3. The adverse reactions to treatment suggest that ipecac is less frequently associated with adverse effects than other methods of inducing emesis. Note that TESS data do not indicate which specific therapy is associated with the adverse reaction to treatment.

Question 5. Were adverse events associated with the use of ipecac?

Response: There were 2,492 cases with an adverse effect to treatment documented in the 434,732 cases that had ipecac administered. While the majority of cases were managed at home, in order to capture all adverse reactions to treatment, cases were included no matter where the treatment site was, a departure from the previous population evaluated in this report (Table 3). This allows inclusion of cases where the ipecac was administered at home and the patient was subsequently treated at a health care facility.

In an additional 8,478 cases, ipecac was listed as the only substance involved in the exposure. The route of exposure was ingestion in 8,363 cases. The number of cases per month appears to be gradually decreasing, although there is significant variation from month to month. The percent of cases that were intentional (abuse, misuse, suspected suicide, or unknown), malicious, or product contamination/tampering also varies by month, and has remained relatively constant over the last 6 years (Figure 6). These cases provide an assessment of the clinical effects and outcomes associated with ipecac ingestion for reasons other than treatment of a poisoning exposure. More than two thirds of the ipecac ingestions are unintentional exposures that may be secondary either to the unintentional ingestion of ipecac by a child. (Table 4) Intentional misuse (1,263) and abuse (586) were the next most common reasons for exposure, and occurred most commonly in patients 13 to 39 years of age. Table 5 shows the outcomes by reason (unintentional, intentional, other, adverse reaction, or unknown). Moderate and major effects were more common in intentional compared to unintentional exposures. One death was reported in 1989 after chronic intentional ipecac administration to a 3 year old.

Question 6. Is there a difference in the recommendation of ipecac based on where the caller lives?

Response: Horowitz et al, in an abstract accepted for presentation at the September, 2004 North American Congress of Clinical Toxicology Annual Meeting (Appendix) describes the frequency of ipecac recommendation for pediatric ingestions by poison control centers based on the caller's county. Designation of county frontier status was based on data from the Frontier Education Center (www.frontierus.org) using population, services, and the county's perspective in assigning frontier county status. The ipecac recommendation rate (number of ipecac recommendations by poison control centers per 1,000 pediatric ingestions) was similar in frontier counties (6.18 ± 13.88) and non-frontier counties (8.51 ± 10.24). The authors suggest that the substance ingested and inter-poison center variation in the use of ipecac may be more significant factors than access to health care services.

Question 7. Is there a consensus among members of the American Association of Poison Control Centers on the use of ipecac?

Response: Figure 7 shows the ranked percentage of ipecac recommended for pediatric exposures, with the call to the poison center coming from a residence, over the 4 year period from January 2000 through December 2003. All poison control centers recommended ipecac in this population during this time period. Overall, ipecac was recommended 30,579 times in 4,113,716 cases (0.74%). Poison control centers had a wide range of ipecac recommendation rates. These findings, and the recent clinical guidelines on ipecac use developed by a consensus panel formed by representatives of AAPCC, ACMT, and AACT that was previously provided to the docket, both suggest that there are divergent views among AAPCC members regarding ipecac use recommendations.

Table 1. AAPCC TESS Data 1989 - 2003: Pediatric Exposures Receiving Ipecac Treatment Reported to US Poison Control Centers. The number of cases that received ipecac (recommended or not recommended by a poison control center), the rank of count, and the percentage of cases in the category that received ipecac. The population consists of pediatric cases managed at home (on site – non-health care facility).

Category	1989-1993			1994-1998			1999-2003		
	Number	Rank	% Cases	Number	Rank	% Cases	Number	Rank	% Cases
Cough/Cold	42,465	1	16.9%	16,889	2	7.5%	6,034	3	2.8%
Analgesics	35,357	2	11.3%	17,341	1	5.7%	7,971	1	2.5%
Mushrooms	17,323	3	68.7%	12,238	3	53.2%	7,021	2	34.9%
Plants	11,581	4	4.8%	7,803	4	2.4%	3,064	5	1.0%
Vitamins	11,581	5	9.4%	7,022	6	5.2%	3,005	7	1.9%
Pesticides	11,046	6	8.0%	7,219	5	5.0%	3,101	4	2.0%
Antihistamines	8,537	7	18.4%	5,784	7	8.9%	3,030	6	2.9%
Antimicrobials	5,711	8	3.7%	2,821	8	1.8%	997	9	0.7%
Cosmetics/personal care products	5,308	9	1.2%	1,735	10	0.3%	1,149	8	0.2%
Gastrointestinal Preparations	5,214	10	4.0%	2,294	9	1.5%	832	10	0.5%
Asthma Therapies	3,632	11	16.5%	1,693	11	6.0%	506	15	1.2%
Electrolytes/Minerals	2,823	12	7.8%	1,324	14	3.6%	410	18	0.9%
Cardiovascular drugs	2,690	13	12.7%	1,228	15	5.4%	523	9	1.8%
Hormones/antagonists	2,606	14	3.7%	1,398	13	1.9%	687	13	0.8%
Stimulants/street drugs	2,536	15	19.9%	1,410	12	8.3%	438	12	3.1%
Cleaning substances (household)	1,718	16	0.4%	1,054	17	0.4%	915	14	0.2%
Antidepressants	816	17	15.1%	1075	16	7.3%	613	17	2.3%
Foreign bodies/etc.	644	18	0.3%	414	18	0.2%	550	11	0.2%
Dietary/herbal homeopathic	236	19	5.0%	212	19	2.0%	432	16	1.4%

Table 2. AAPCC TESS Data 2000 - 2003: Cases with Ipecac therapy Recommended by US Poison Control Centers. The number of cases that received ipecac after it was recommended by a poison control center SPI and the percentage of cases in the category that received ipecac. The population consists of pediatric cases managed at home (on site – non-health care facility management site).

Category	Cases with Ipecac Recommended	Percentage of Cases with Ipecac Recommended
Cough/Cold	4,385	1.6%
Analgesics	5,731	1.4%
Mushrooms	5,157	21.5%
Plants	2,060	0.5%
Vitamins	2,245	1.3%
Pesticides	2,190	1.2%
Antihistamines	702	2.7%
Antimicrobials	930	0.3%
Cosmetics/personal care products	607	0.1%
Gastrointestinal Preparations	404	0.3%
Asthma Therapies	286	0.9%
Electrolytes/Minerals	286	0.5%
Cardiovascular drugs	405	1.0%
Hormones/antagonists	531	0.4%
Stimulants/street drugs	322	1.2%
Cleaning substances (household)	761	0.0%
Antidepressants	495	2.1%
Foreign bodies/etc.	459	0.0%
Dietary/herbal Homeopathic	373	2.2%

Table 3. AAPCC TESS Data 1989 - 2003: Medical Outcomes Associated with Ipecac Treatment and Other Emetic Treatment, and Adverse Reactions to Treatment reported as a Clinical Effect Reported to US Poison Control Centers. All cases with the initial caller site not a health care facility were included in order to obtain outcomes in all cases where home ipecac or other emetic administration was performed, including those that may have been evaluated and treated at a health care facility..

Outcome		Ipecac	Percent	Other Emetic Therapy	Percent
Total Cases		434,733		37,904	
None		327,659	75.4%	15,291	40.3%
Minor		46,932	10.8%	5,039	13.3%
Moderate		2,340	.01%	357	0.9%
Major		82	0.0%	38	0.1%
Death		0	0.0%	4	0.0%
No follow-up		54,137	12.5%	16,098	42.5%
Unrelated effect		3,623	0.8%	1,077	2.8%
Clinical Effect					
ADR to treatment		2,492	0.0%	333	0.9%

AAPCC Toxic Exposure Surveillance System (TESS)

**Table 4. AAPCC TESS - Poison Exposures with Ipecac Coded as Substance Ingested, rather than as Treatment.
1989 - 2003**

Reason by Age (Adults in Decades)

	<6	6-12	13-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>=90	Unk Child	Unk Adult	Unknown	Missing/ Invalid	Total
Unintentional																
General	4,100	130	160	233	111	64	22	8	7	2	0	9	106	36	0	4,988
Environmental	3	0	0	0	0	0	0	0	0	0	0	0	0	1	0	4
Occupational	0	0	0	2	1	1	0	0	0	0	0	0	0	0	0	4
Therapeutic error	225	48	53	72	47	24	6	3	2	2	0	0	33	3	0	518
Misuse	144	26	65	94	87	36	14	6	3	4	0	0	47	10	0	536
Bite / sting	0	0	1	0	0	2	0	0	0	0	0	0	0	0	0	3
Food poisoning	1	0	0	2	5	1	0	0	0	0	0	0	0	0	0	9
Unknown	4	2	1	3	2	2	0	0	0	0	0	0	5	2	0	21
Subtotal	4,477	206	280	406	253	130	42	17	12	8	0	9	191	52	0	6,083
Intentional																
Suspected suicide	1	1	25	20	5	1	2	1	0	0	0	0	6	3	0	65
Misuse	35	56	387	340	160	55	18	17	2	2	0	0	159	32	0	1,263
Abuse	7	9	239	168	58	16	6	0	0	0	0	3	64	16	0	586
Unknown	5	13	25	27	12	5	3	0	1	0	0	0	20	6	0	117
Subtotal	48	79	676	555	235	77	29	18	3	2	0	3	249	57	0	2,031
Other																
Contamination / tampering	2	2	4	2	2	3	0	0	0	1	0	0	1	0	0	17
Malicious	36	21	52	29	20	9	3	5	1	1	0	1	14	2	0	194
Withdrawal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Subtotal	38	23	56	31	22	12	3	5	1	2	0	1	15	2	0	211
Adverse reaction																
Drug	28	2	7	16	9	9	4	1	0	0	0	1	10	1	0	88
Food	1	0	1	0	0	2	0	0	0	0	0	0	0	0	0	4
Other	0	0	0	1	3	0	1	0	0	0	0	0	0	1	0	6
Subtotal	29	2	8	17	12	11	5	1	0	0	0	1	10	2	0	98
Unknown																
Unknown reason	12	15	10	6	2	2	0	0	0	0	0	0	4	4	0	55
Subtotal	12	15	10	6	2	2	0	0	0	0	0	0	4	4	0	55

AAPCC Toxic Exposure Surveillance System (TESS)

**Table 4. AAPCC TESS - Poison Exposures with Ipecac Coded as Substance Ingested, rather than as Treatment.
1989 - 2003**

Reason by Age (Adults in Decades)

	<6	6-12	13-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	>=90	Unk Child	Unk Adult	Missing/ Invalid	Total	
Total	4,604	325	1,030	1,015	524	232	79	41	16	12	0	14	469	117	0	8,478

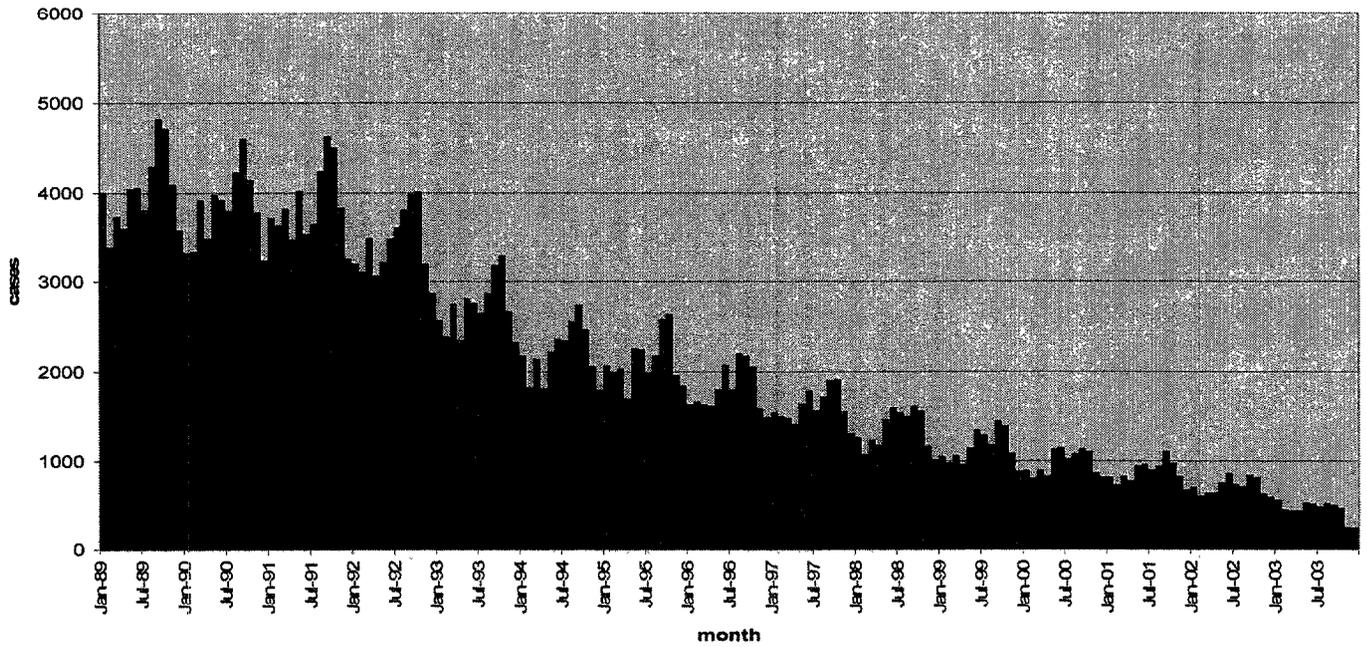
AAPCC Toxic Exposure Surveillance System (TESS)

**Table 5. AAPCC TESS - Poison Exposures with Ipecac Coded as Substance Ingested, rather than as Treatment.
1989 - 2003**

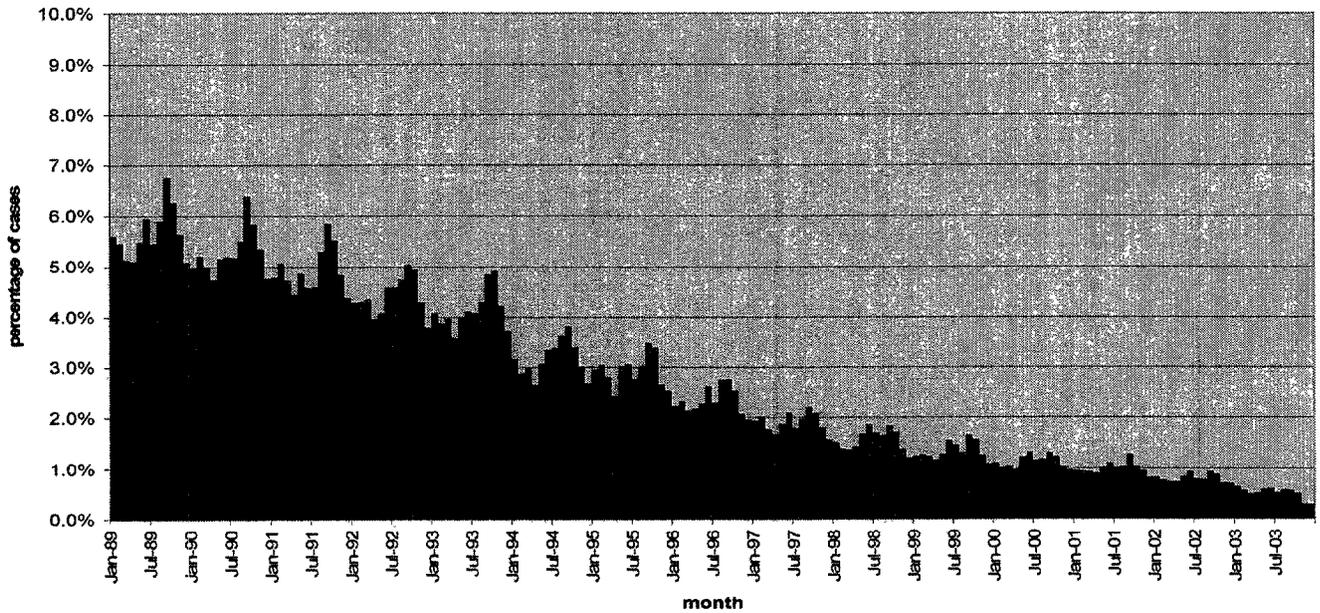
Medical Outcome by Reason

	Unintentional		Intentional		Other		Adverse Reaction		Unknown		Invalid/Missing		Total	
	No	Row %	No	Row %	No	Row %	No	Row %	No	Row %	No	Row %	No	Col %
No effect	1,371	92.57	100	6.75	5	0.34	3	0.20	2	0.14	0	0.00	1,481	17.47
Minor effect	2,431	76.23	632	19.82	85	2.67	29	0.91	12	0.38	0	0.00	3,189	37.62
Moderate effect	57	45.60	52	41.60	8	6.40	4	3.20	4	3.20	0	0.00	125	1.47
Major effect	2	20.00	2	20.00	5	50.00	0	0.00	1	10.00	0	0.00	10	0.12
Death	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.01
Death, indirect report	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
No follow-up, nontoxic	626	78.94	153	19.29	3	0.38	8	1.01	3	0.38	0	0.00	793	9.35
No follow-up, minimal toxicity	1,271	64.19	591	29.85	69	3.48	32	1.62	17	0.86	0	0.00	1,980	23.35
No follow-up, potentially toxic	239	32.92	449	61.85	20	2.75	5	0.69	13	1.79	0	0.00	726	8.56
Unrelated effect	86	49.71	51	29.48	16	9.25	17	9.83	3	1.73	0	0.00	173	2.04
Subtotal for exposures	6,083	71.75	2,031	23.96	211	2.49	98	1.16	55	0.65	0	0.00	8,478	100.00
Confirmed nonexposure	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	6,083	71.75	2,031	23.96	211	2.49	98	1.16	55	0.65	0	0.00	8,478	100.00

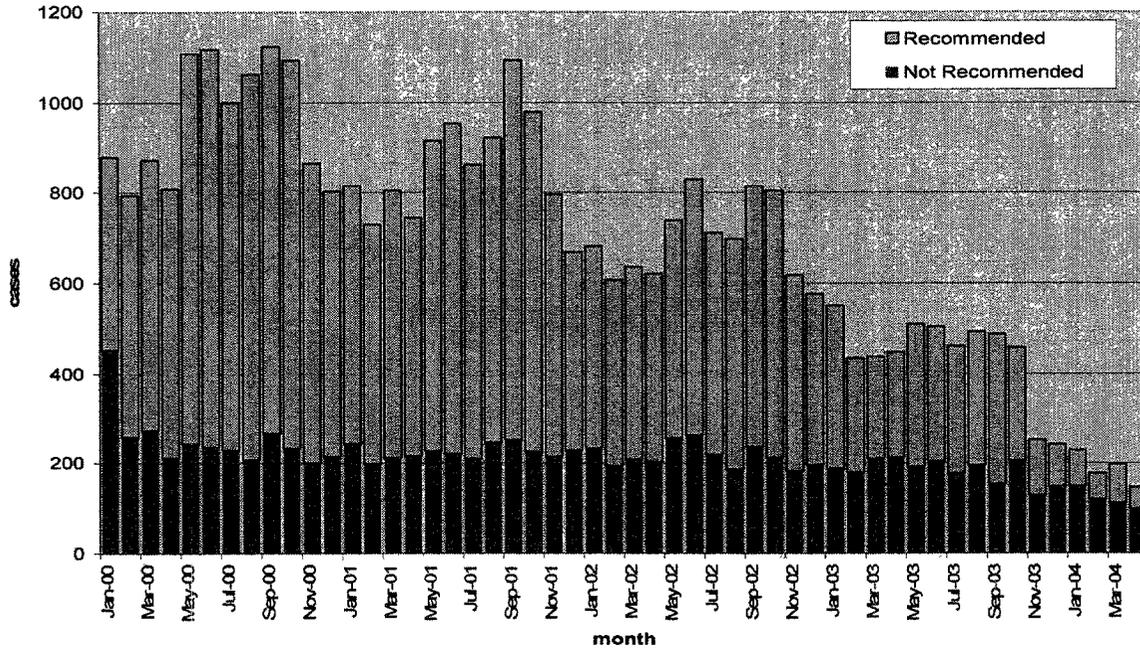
**Figure 1. AAPCC TESS - Pediatric Exposures Treated with Ipecac.
1989 - 2003**



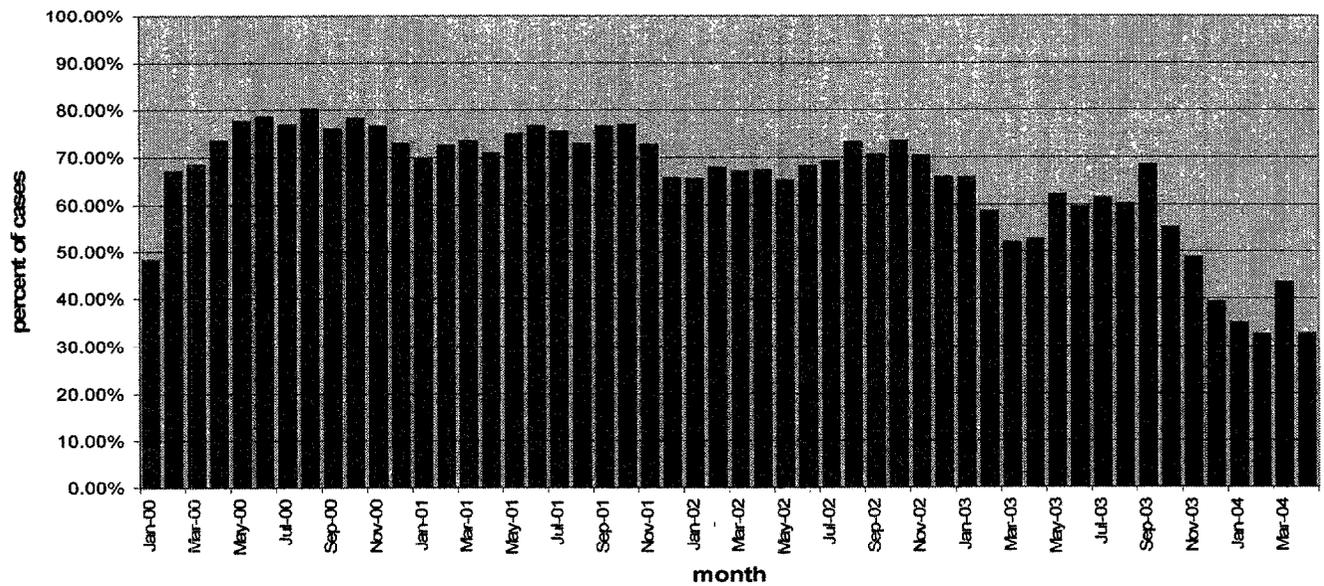
**Figure 2. AAPCC TESS - Percent of Pediatric Exposures Treated with Ipecac
and Managed on Site (non-health care facility).
1989 - 2003**



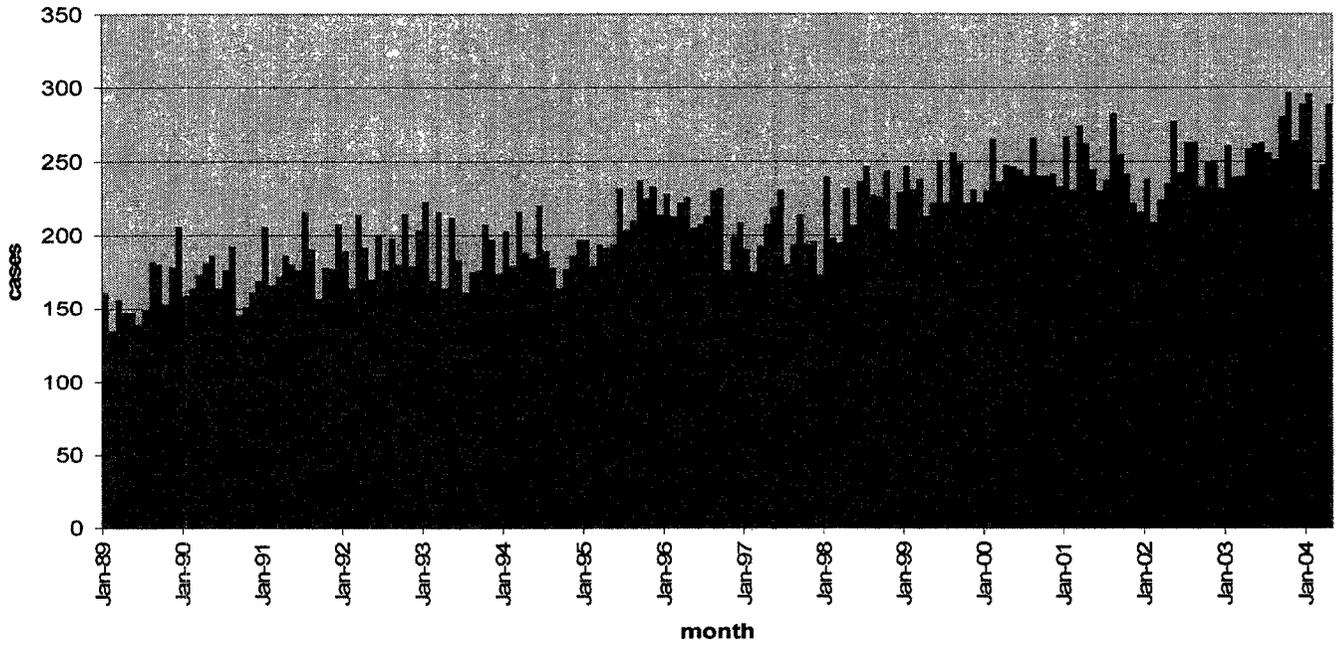
**Figure 3. AAPCC TESS - Ipecac Administration Recommended by Poison Control Center
January 2000 through April 2004**



**Figure 4. AAPCC TESS - Ipecac Administration
The Percent Recommended by Poison Control Centers
January 2000 through April 2004**



**Figure 5. AAPCC TESS - Emetic Use Other than Ipecac Syrup
1989 - 2003**



**Figure 6. AAPCC TESS - Ipecac Poisoning Exposures and Reason for Exposure
1989 - 2003**

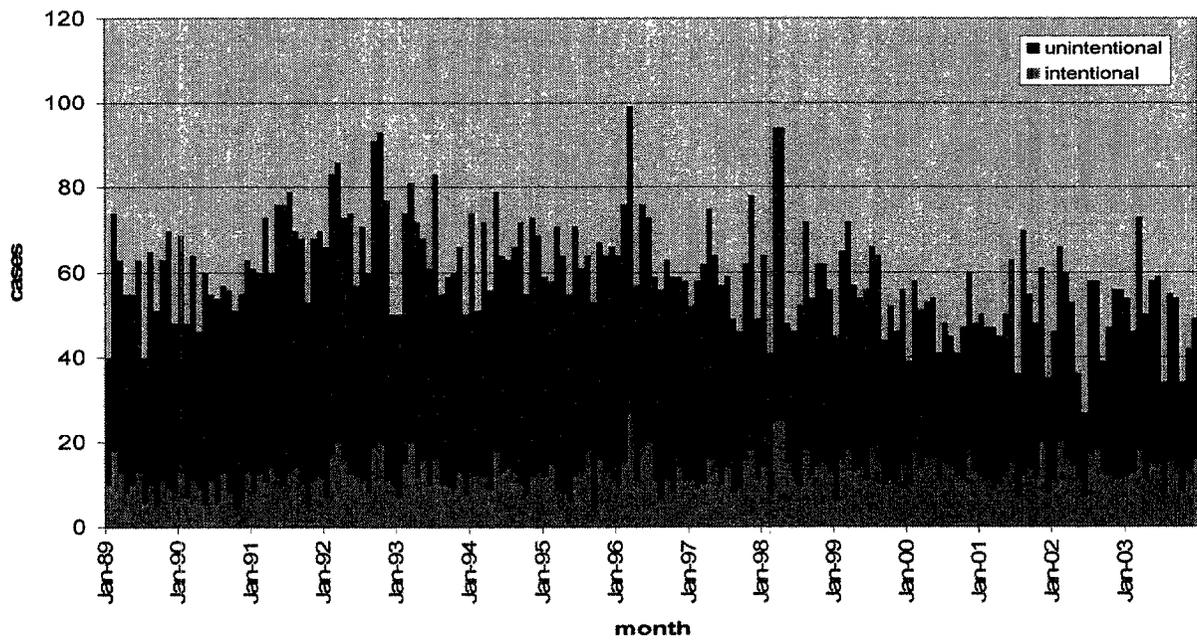
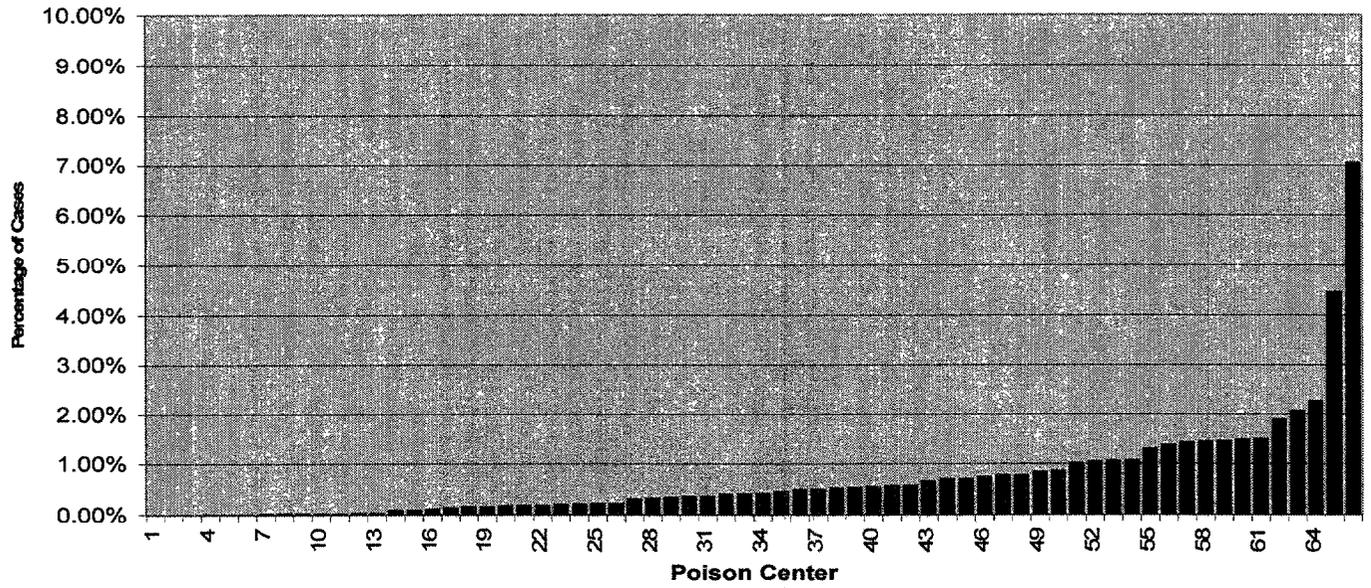


Figure 7. AAPCC TESS - Comparison of Poison Center Recommendation of Ipecac for Pediatric Ingestions with Call From Residence (Ranked by Poison Center Recommendation Frequency) 2000-2003



Appendix

IPECAC: POPULATION DENSITY, FRONTIER DESIGNATION, AND POISON CENTER RECOMMENDATIONS

Horowitz Z, Watson W, Reid N, Litovitz T, Oregon-Alaska Poison Center, Portland, OR, and the American Association of Poison Control Centers, Washington, DC

Background: In November 2003 the American Academy of Pediatrics recommended that ipecac no longer be considered for routine home management of pediatric poisoning. Some toxicologists believe ipecac may continue to play a role in remote regions of the country with limited access to health care facilities. **Methods:** A review of the AAPCC TESS database for 2000 through 2003 was done. All ingestions by children < 6 years of age were included. The ipecac recommendation ratio (IRR) was calculated as the number of recommendations per 1000 ingestions where the poison center recommended ipecac use. Actual administration of ipecac was not a study criterion. The IRR by county population density was compared among population density quartiles, and by frontier vs. non-frontier county categories [Frontier Education Center (FEC) definition (www.frontierus.org)]. **Results:** The mean county IRR was 7.91 ± 11.18 (SD). The mean IRR by county for the 4 inter-quartile population density ranges, ranked from lowest to highest population density ranges, were similar (6.49 ± 13.54 ; 9.00 ± 11.65 ; 8.12 ± 9.87 ; 8.04 ± 8.98). In 492 (61%) of frontier counties, ipecac was not recommended; in 315 counties ipecac was recommended at least once; 3 frontier counties had no pediatric ingestions. Frontier counties had an IRR of 6.18 ± 13.38 and non-frontier counties had an IRR of 8.51 ± 10.24 . **Conclusions:** Population density and designation as a frontier county did not appear to impact the frequency of poison center recommendation of ipecac between 2000 and 2003. The substance involved and inter-poison center variations in use of ipecac syrup may be more significant factors than access to health care services.