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Food and Drug Administration
Department of Health and
Human Services
Room 4-62
5600 Fishers Lane
Rockville, Maryland 20857

CITIZEN PETITION

The undersigned submits this petition on behalf of Thompson Medical Company, Inc. under 21 CFR 10.30 to request the Commissioner of Food and Dugs to open the administrative records in the Over-the-Counter Drug Reviews of Weight Control Drug Products (Docket No. 81N-0022) and Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Docket No. 76N-0052N) to accept the enclosed materials relating to the recently-published study conducted at the Intermountain Regional Poison Control Center and Department of Pharmacy Practice, University of Utah, Salt Lake City, Utah.

A. Action Requested

The undersigned respectfully requests that the administrative record be opened to permit the enclosed materials to be considered in the referenced OTC Drug Review.

B. Statement of Grounds

The grounds on which petitioner relies are that phenylpropanolamine hydrochloride (PPA) is one of the ingredients of weight control products and nasal decongestants which are the subjects, respectively, of the above-referenced proposed OTC Drug Products Monographs. The Panel Monographs concluded that PPA and its salts are

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safe and effective for OTC weight control and oral nasal decongestant use in the specified dosages. The Tentative Final Monograph has not yet been published in either Review. In the preamble to the Advance Notice of Proposed Rulemaking in the Weight Control Drug Products Review (47 Fed. Reg. 8466, et seq., February 25, 1982), the Commissioner requested further studies regarding the safety of PPA for use in weight control products.

The enclosed materials summarize a study demonstrating the safety of PPA in weight control products. Since the same ingredient is involved in both types of products, the enclosed materials are highly significant to the agency's OTC Drug Reviews of both weight control and cough/cold drug products. Therefore, these materials should be considered in both Reviews at the earliest possible time

C. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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SCIENTIFIC REPORTS

Papers published in this section are reviewed by at least two qualified referees for accuracy, scientific soundness, experimental des data analysis, and interpretation. Papers accepted may result from original research, critical literature reviews or well documented f investigations.

AN ESTIMATION OF THE TOXICITY OF NON-PRESCRIPTION DIET AIDS FROM SEVENTY EXPOSURE CASES

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The American compulsion to be slim, combined with the conclusions of a non-government advisory panel's recommendations in March of 1979 indicating benzocaine and phenylpropanolamine (PPA) in over-the-counter (OTC) weight control products to be safe and effective, have increased the use and the availability of these drugs in American homes. Weight control products obtained without a prescription fall into two classes: sympathomimetic-containing products and those without. Those without may contain vitamins, methylcellulose, benzocaine, fructose, lethicin, and grapefruit extract. The sympathomimetic-containing weight control products may contain any of the above with PPA alone or combined with caffeine. Table 1 lists some of the common commercially available products. While PPA is reported safe in doses for weight control (1), there are limited data about the toxic effects of PPA when taken in overdose (2-5). There is mounting evidence of serious toxicity when taken in combination with other drugs (6-8) and in hypersensitive persons using normal doses (9-20). Caffeine is not an innocuous drug (12,22). Although serious toxicity from caffeine is rare, its danger is well documented (23-28). Caffeine in combination with PPA will contribute to the toxicity in possibly both overdosage and in regular doses.

The purpose of this report is to describe the range of presenting signs and symptoms following ingestion of OTC sympathomimetic-containing weight control products and to estimate the toxic dose and sequelae from such overdose.

METHODS

The patients for this prospective study were either children or adults who had ingested a non-proprietary sympathomimetic-containing weight control product. The study period was for 5 months. Patients who met the following criteria were included: History of ingestion of a sympathomimetic-

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Table 1. Commonly Available Over-The-Counter Stimulant-Containing Appetite Suppressant Products

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Substances
Anorexin Pick Your Menu Weight Loss Program				
Anorexin	SDA Pharm	25	100	--
Anorexin One-Span	SDA Pharm	50	200	--
Appedrine Max Strength	Thompson Medical	25	100	+
Appress Tablets	North American	25	100	--
Ayds Appetite Suppressant Droplets (0.6 ml=12 drops)	Purex	25	0	--
Ayds Extra Strength (Red Capsule)	Purex	75	200	--
Ayds AM/PM Appetite Suppressant Capsules	Purex			
Yellow Cap.		50	200	--
Blue Cap.		25	0	--
Cenadex Capsules	Central	75	200	--
Codexin	Arco Pharm	75	200	→
Coffee Break Cubes Weight Reduction Plan	O'Conner Drug	37.5	0	--
Coffee-Off	Westport Pharm Sales	25	0	--
Coffee, Tea, and a New Me	Thompson Medical	25	0	--
Control Capsules	Thompson Medical	75	0	--
Control Drops/0.2 ml=4 drops	Thompson Medical	25	0	--

Table 1 (cont)

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Substances
Cool Down Tablets	Westpoint Pharm Sales	25	0	--
Day Trim	Westpoint Pharm Sales	75	0	--
DelcoPro Tablets	Delco	25	0	--
Capsules		75	0	--
Dexa-Dar Capsules	Republic Drug	50	200	--
Dexadar Plus	Republic Drug	75	200	--
Dex-A-Diet Capsules (formerly Dex-A-Diet II)	O'Conner Drug	75	200	--
Dex-A-Diet Drops (formerly Dex-A-Diet II)/0.6 ml	O'Conner Drug	25	0	--
Dex-A-Diet Lite Capsules	O'Conner Drug	75	0	--
Dexatrim Capsules	Thompson Medical	50	200	--
Dexatrim Ex Strength Capsules	Thompson Medical	75	200	--
Dexatrim Caffeine-Free Ex Strength Capsules	Thompson Medical	75	0	--
Diadax Capsules	O'Conner Drug	50	0	--
Tablets		25	0	--
Dietac Pre-Meal Diet Aid Drops/0.2 ml = 5 drops	Menley James Labs	25	0	--
Dietac Pre-Meal Diet Aid Tablets	Menley James Labs	25	0	--
Dietac 12 Hr Diet Aid Capsules	Menley James Labs	50	200	--
Dietac Max Strength Capsules	Menley James Labs			
Once-A-Day		75	0	--
Twice-A-Day		37.5	0	--
Dietcap	L Perrigo	50	200	--
Dietcap without Caffeine	L Perrigo	75	0	--
Dietguard 14 Day Diet Plan	Whitehall Lab	25	0	--
Diet Trim	Pharmex	Present Amount?	0	+
Dyna-Slim WL	Weight Loss Group	75	0	--

Table 1 (cont)

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Substances
Fluidex Plus	O'Conner Drug	25	0	+
Grapefruit Chewable Diet Tablets	Sharpe Nationals	60	0	+
Grapefruit Diet Plan With Diadax Tablets	O'Conner Drug			
Capsules		10	0	+
		30	0	+
Grapefruit Diet Plan With Diadax Chewable Tablets Ex Strength	O'Conner Drug	25	0	+
Grapefruit Diet Plan With Diadax Ex Strength Vitamin Fortified Continuous Action Capsules	O'Conner Drug	75	0	+
Hungrex	Alleghany Pharmacal	25	0	--
Hungrex Plus	Alleghany Pharmacal	33.33	66	--
Obestat	Lemmon	75	0	--
Odrinex - See Super Odrinex				
Permathene-12	Alleghany Pharmacal	75	140	--
Phenopro-75 Ex Strength	M K Lab	75	200	--
PPA - Max Strength	Alleghany Pharmacal	75	0	--
Pro-Dax 21	O'Conner Drug	75	0	--
Prolamine Capsules	Thompson Medical	37.5	140	--
PVM Appetite Control Capsules	J B Williams	75	0	--
PVM Appetite Suppressant	J B Williams	25	0	--
Sip and Slender	Alleghany Pharmacal	25	0	--
Slimplan Ex Strength Plus	Whitworth	75	200	--
Spantrol	North American	45	50	+
Spantrol Ex Strength Plus	North American	75	150	+
Super Odrinex	Fox Pharmacal	25	100	--

Table 3. Symptoms, Treatment and Dosage of Phenylpropanolamine/Caffeine Combination by Age

Age	Total	Symptomatic Number (%)	Onset of Symptoms (hr)	Duration (hr)	Estimated Dose Ingested By Symptomatic Patients				Ipecac Given	No Treatment
					PPA		Caffeine			
					mg	mg/kg	mg	mg/kg		
0-2	19	3 (15.8)	2	2-4	133	10.5	460	40	9	10
3-5	14	2 (14)	<1	3	150	9.8	500	34	3	11
6-12	2	1 (50)	<2½	12	300	8.2	800	22	0	2
13-21	19	19 (100)	1	12±9.48	575	8.8	1400	26	5	10
>22	7	6 (85.7)	1½	20±14.5	235	5	680	15	1	4

only 1-2 dosage units.

The type of symptoms and frequency noted in the study patients are listed in Table 4. Headache, nausea or vomiting, nervousness, and tachycardia were most often seen. Almost all symptoms appeared within the first two hours. In approximately one-third of the cases, symptoms persisted for up to 6 h, another one-third of the cases had symptoms for up to 10 to 12 h, and the remaining one-third had symptoms persisting for widely varying lengths of time.

Physician evaluation was required only 16 times (22.85%). Seventy-seven percent of the time the problem was managed at home with only demulcents to delay absorption or the induction of emesis using syrup of ipecac. Of the patients managed in the hospital, only two required hospitalization, 64% were discharged from the emergency department in less than 4 h, and the remaining discharged in an average of 8.25 h. The duration of treatment in the health care facility and the therapy performed are noted in Table 5.

DISCUSSION

Phenylpropanolamine is a sympathomimetic amine structurally similar to amphetamine, ephedrine and metaraminol. The pharmacologic actions of PPA are described as a direct alpha adrenergic effect and an indirect acting amine producing release of norepinephrine from storage site at nerve endings (8,11). Its structural formula protects it from rapid degradation allowing for extended duration of action from oral admini-

stration (20). Common side effects from overdose associated with PPA include hypertension (2,4,12-14,19,20), severe headaches (2,4,11-13,19), blurred vision (13), confusion (4,5,13,16,18,19), vomiting (2,12,19), and seizures (2,5,13,20).

Caffeine is a naturally occurring alkaloid which is rarely associated with serious adverse reactions or fatalities (22). A possible explanation for the low frequency of serious reactions is the high incidence of gastritis and prominent central nervous system side effects with relatively small doses. Pharmacologic effects on the central nervous and digestive systems can be seen with as little a dose as 50 mg. A therapeutic dose is near 100-200 mg (27). Caffeine stimulates the cerebral cortex, the thalamus, the vasomotor and respiratory centers (21, 22,24-27). Cardiac stimulation resulting in a variety of arrhythmias have been reported (21,23,25). The combination of caffeine with PPA produces a pharmacologic synergism accentuating some action of each drug.

The dose at which symptoms developed for PPA alone was 17.5 mg/kg. This is not suggestive of a minimum toxic dose, rather a dose that predictably produced symptoms in the study patients. When PPA/caffeine combinations were involved in children (age 0-5), a toxic dose for PPA was close to 10 mg/kg (average total dose was 140 mg). The caffeine doses averaged 37 mg/kg with an average total dose of 480 mg producing symptoms. All adults studied were symptomatic, suggesting that early demonstrable clinical findings are expected and that symptoms are not a good early discriminator between the low versus the high end of toxicity.

Table 4. Symptom Complaint and Frequency

Symptom (May be more than one symptom per case)	No
Nausea or vomiting	20
Nervousness	12
Headache	10
Tachycardia	8
Dizziness	6
Drowsiness	3
Weakness	3
Disorientation	2
Shortness of breath	2
Hot flashes	1
Increased urination	1
Flushed	1
Numbness of hands	1

Table 5. Treatment Performed and Duration of Time in the Health Care Facility (Number)

Duration of Time in the Health Care Facility (hr)		
<4		9
4-8		4
8-14		1
>14		2
Treatment Performed		
Ipecac		9
Activated Charcoal		5
Cathartic		4
Intravenous hydration		3
Phenobarbital		1

Table 1 (cont)

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Substances
Thinz Drops/ 1 ml=5 drops	Alva Amco Pharmacal	25	0	+
Thinz Back- To-Nature Tablet Reduc- ing Plan - Ex Strength Formula	Alva Amco Pharmacal	75	+	--
Thinz-Span Max Strength	Alva Amco Pharmacal	75	+	--
Trim Down	Ajem Drug	75	0	--
Unitrol Diet Plan Capsules	Republic Drug	75	0	--
Vita Slim Capsules	Thompson Medical	50	0	+
X-11 Reduc- ing Plan Tablet	Porter and Dietsch	25	25	+

containing weight control product, subsequent treatment, follow-up or evaluation by the poison control center staff or at a treatment facility. All ages were included. For patients evaluated and treated at home, telephone contact was maintained to resolution of symptoms or for twelve hours, whichever was longer. Patients were excluded from the study for the following reasons: ingestion of significant amounts of other drugs concomitant with the study drugs, lack of satisfactory history, and patients whose condition was later determined to be of another origin.

RESULTS

During the five months of the study, a total of 70 patients met the criteria of the study. The data from these patients form the basis of this report. Thirty-four percent of the patients were male (24) and 65% were female (46) despite a mean even sex ratio in the 0-5 age group. The ages studied ranged from 9 m to 20 y (mean 5.0 y, SD = 5.74 y) for males, and 1½-54 y (mean 13.4 y, SD 12.1 y) for females.

The patients were divided into two groups: Those involved with accidental childhood ingestion (9 m to 8 y) and the self-destructive or substance abuse patients (age 11-54 y). The ages and sex ratios of the former group were near equal with no striking differences. In the intentional group there is a 1:6.5 ratio of males to females and a distribution of ages in females which indicates the misuse of these substances is not limited to a discrete age group. The preponderance of females using these substances compared to males may be indicative of the more likely purchaser of diet aids. Young adults (ages 13-21 y) comprised 30% of all cases and almost 75% of the intentional group. Children ages 0-5 accounted for 56% of all cases seen.

Table 2 is a list of the non-proprietary products involved in the 70 cases. In some cases several products were involved. Dexatrim® (regular or extra-strength) products accounted for 71.4% of all the products involved suggesting ready availability in the homes from either advertising or sales success.

Both Dexatrim® products are combinations of PPA and caffeine. Ten cases (14.3%) involved only PPA, the remaining 60 cases (85.7%) involved combinations of both PPA and caffeine in varying doses and amounts. No products with only caffeine were involved.

None of the PPA-only cases involving children under 14 developed symptoms although small amounts were generally ingested. All of the patients over 14 who ingested only PPA developed mild symptoms. The symptoms described in these four patients included nausea, vomiting, abdominal cramps, headache, hot flashes, diaphoresis, dyspnea, irritability and tachycardia (140 beats/min). In patients with only PPA involved, the onset of symptoms was usually within 30 min to 1 h and the duration of symptoms averaged 13 h. Only one patient required hospitalization. An estimated ingested dose in the symptomatic patients was 17.5 mg/kg.

The fixed dosage ratios of PPA to caffeine (Table 1) ranges from a low of 1:1 to a high of 1:4. Therefore, at a given dose of PPA the amount of caffeine present in the product may vary by a factor of four. This makes defining the dosages of either PPA or caffeine in combination difficult with the available data. Table 3 describes symptomatic patients by age with the estimated doses of PPA and caffeine ingested and the dose to weight relationship. All patients over age 13 were symptomatic regardless of the history of ingestion. Children in the 0-2½ y age range generally took

Table 2. Brands of Diet Aids Involved in Seventy Human Poisonings.

Brand Name	Exposures	%
Appedrine Maximum Strength	1	1.4
Control	5	7.1
Dex-A-Diet 11	1	1.4
Dexatrim	29	41.4
Dexatrim Extra Strength	21	30.0
Dietac:	6	8.6
Pre-Meal Diet Aid Tablets	1	
Maximum Strength Once-A-Day	1	
Pre-Meal Diet Aid Drops	1	
12 Hour Diet Aid	3	
Hungrex	1	1.4
Permathene-12	1	1.4
Phen-Pro-75	1	1.4
Super Odrinex	1	1.4
X-11	2	2.9
Unknown	1	1.4

The lack of serious side effects in either the cases with only PPA or combinations of PPA with caffeine raises questions about the serious reactions noted in earlier published reports. The Bureau of Drugs/FDA is currently preparing a report on serious morbidity and mortality associated with diet pills containing PPA, caffeine, and ephedrine, singly or in combination with each other (Kawazo HE: Personal Communications. FDA, February 1982). The discrepancy in the severity of reactions in the FDA report and the current study suggests many questions. The incidence of such reactions, their mechanisms of action and the true hazard to the community from such products remains to be addressed.

The popularity of OTC diet aids will likely continue to produce significant numbers of ingestions, both accidental and intentional. The results of this study indicate the majority of overdoses involving OTC diet aids will not be serious and may only require decontamination of the digestive tract and supportive care. We recommend that emesis be induced with reported ingestions of diet aids involving more than 8-10 mg of PPA in children. Deliberate ingestions by adults require careful consideration of the history of ingestion, the agents involved, and the intent of the victim. In most cases, emesis should be induced in all adult poisonings unless there is strong evidence not to. In children a dose of 8-10 mg/kg would be expected to produce only mild symptoms; however, the impact and trauma of forced emesis is considered less hazardous and preferable to allowing a victim to develop even mild symptoms. The use of this dose as a cut-off for the induction of emesis is consistent with our clinical impression that amounts of PPA below this quantity are well tolerated and are not expected to result in any more serious side effects. Obviously, if the history of ingestion cannot reliably be ascertained treatment should be performed. Physicians and poison control centers should recognize that these agents can produce life-threatening cardiac arrhythmias, hypertension, and other serious effects.

The challenge to pharmacists and physicians is to educate the consuming public to the safety and proper use of these and other substances for weight reduction. Treatment of serious adverse reactions or overdosage with OTC diet aids will continue to be a clinical problem as long as the public demand for this method of weight control remains constant.

REFERENCES

1. Anon: The new diet pills. *Consumer Reports* 1: 14-16, 1982.
2. Patterson FK: Delayed fatal outcome of after possible Ru-tuss[®] overdose. *J Forensic Sci* 25: 349-352, 1980.
3. Duffy WB, Senekjian HO, Knight TF, et al: Acute renal failure due to phenylpropanolamine. *South Med J* 74:1548-1549, 1981.
4. Salmon PR: Hypertensive crisis with Eskornade.

Br Med J 1:195, 1975.

5. Korvenius G, Wigerlov E, Lonnerholm G: Phenylpropanolamine and mental disturbances. *Lancet* 2:1367-1368, 1979.
6. Cuthbert MF, Greenberg MP, Morley SW: Cough and cold remedies: a potential danger to patients on monoamine oxidase inhibitors. *Br Med J* 1: 404-406, 1969.
7. McLaren EH: Severe hypertension produced by interaction of phenylpropanolamine with methyl dopa and oxprenolol. *Brit Med J* 2:283-284, 1976.
8. Lee KY, Beilin LJ, Vandongen R: Severe Hypertension after ingestion of an appetite suppressant (phenylpropanolamine) with indomethacin. *Lancet* 1 (8126):1110-1111, 1979.
9. Peterson RB, Vasquez LA: Phenylpropanolamine-induced arrhythmias. *JAMA* 223(3):324-325, 1973.
10. Speer F, Carrasco LC, Kimura CC: Allergy to phenylpropanolamine. *Annals Allergy* 40(1):32-34, 1978.
11. Horowitz JD, McNeil JJ, Sweet B, et al: Hypertension and postural hypotension induced by phenylpropanolamine (Trimolets). *Med J Aust* 1: 175-176, 1979.
12. Bennett WM: Hazards of the appetite suppressant phenylpropanolamine. *Lancet* 2 (8132):42-43, 1979.
13. Deocampo PD: Convulsive seizures due to phenylpropanolamine. *J Med Soc NJ* 76:591-592, 1979.
14. King J: Hypertension and cerebral hemorrhage after trimolets ingestion. *Med J Aust* 2:258, 1979.
15. Horowitz JD, Lang WJ, Howes LG, et al: Hypertensive responses by phenylpropanolamine in anorectic and decongestant preparations. *Lancet* 1 (8159): 60-61, 1980.
16. Schaffer CB, Pauli MW: Psychotic reaction caused by proprietary oral diet agents. *Am J Psychiat* 137:1256-1257, 1980.
17. Dietz AJ: Amphetamine-like reactions to phenylpropanolamine. *JAMA* 245:601-602, 1981.
18. Achor MB, Extein I: Diet aids, mania, and affective illness. *Am J Psychiat* 138:392, 1981.
19. Elliott CF, Whyte JC: Phenylpropanolamine and hypertension. *Med J Aust* 1:715, 1981.
20. Bernstein E, Diskant BM: Phenylpropanolamine: a potentially hazardous drug. *Ann Emerg Med* 11: 311-315, 1982.
21. Turner JE, Cravey RH: A fatal ingestion of caffeine. *Clin Tox* 10(3):341-344, 1977.
22. McGee MB: Caffeine poisoning in a 19 year old female. *J Forensic Sci* 25(1):29-32, 1980.
23. Josephson GW, Stine RJ: Caffeine intoxication: a case of paroxysmal atrial tachycardia. *JACEP* 5:776-778, 1976.
24. Sullivan JL: Caffeine poisoning in an infant. *J Peds* 90(6):1022-1023, 1977.
25. Kulkarni PB, Dorand RD: Caffeine toxicity in a neonate. *Pediatrics* 64(2):254-255, 1979.
26. Shen WW, D'Souza TC: Cola-induced psychotic organic brain syndrome. *Rocky Mt Med J* 76(6):312-313, 1979.
27. Banner W, Czajka PA: Acute caffeine overdose in the neonate. *Am J Dis Child* 134:495-498, 1980.
28. May DC, Long T, Madden R, et al: Caffeine toxicity secondary to street drug ingestion. *Ann Emerg Med* 10:549, 1981.