



THE PROPRIETARY ASSOCIATION

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August 27, 1982

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Dockets Management Branch (HFA-305)
Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Reply Comments: Weight Control Drug Products
for Over-the-Counter Human Use; Establishment of
a Monograph; Advance Notice of Proposed
Rulemaking, 47 Fed. Reg. 8466 et seq.
(February 26, 1982), Docket No. 81N-0022

Dear Sir:

Comments were due on July 26, 1982, on the above proposal, which consists of a Report and Proposed Monograph of the Advisory Panel on OTC Miscellaneous Internal Drug Products, convened by the Food and Drug Administration under its OTC Drug Review. Reply comments were to be submitted by August 27, 1982.

These reply comments are filed on behalf of The Proprietary Association, a 101-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription or over-the-counter medicinal products. Members of the Association are subject to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301, et seq.) and are interested in and affected by this proposal.

These reply comments are not intended to supersede any which may be filed by individual members of the Association.

Comments Which Assert that Phenylpropanolamine Causes High Blood Pressure or Other Adverse Reactions.

The principal concerns of the Center for Science in the Public Interest (CSPI) regarding the safety of

phenylpropanolamine rest on what CSPI describes as "the known tendency of PPA to raise blood pressure...." (CSPI, p. 5.) To the contrary, there have been no studies submitted or cited by any participant in this proceeding that support the proposition that PPA has a "known tendency" to raise blood pressure at the dosage levels recommended in the ANPR.

In its discussion of the relationship between PPA and hypertension, CSPI states that after the Panel's report on weight control products containing PPA was submitted to FDA in 1979 "several reports of alarming cardiovascular reactions to recommended quantities of PPA appeared in the the medical literature." (CSPI, p. 6.) "In response to this evidence," CSPI goes on to state, "FDA took regulatory action to remove from the market all weight control products containing single, immediate-release doses of greater than 37.5 mg of PPA and timed-release doses of greater than 75 mg." (CSPI, p. 6.) This is incorrect. In actuality the action by FDA to limit products to single, immediate-release doses of not greater than 37.5 mg of PPA and timed-release doses of not greater than 75 mg was based on the agency's position that products which contained higher doses were not marketed OTC prior to December 5, 1975, and were, therefore, "new drugs." (47 Fed. Reg. 8469, February 26, 1982.)

CSPI cites the double-blind trial reported by Horowitz, et al., in 1980 as substantiation for its assertion that the available evidence does not support a Category I classification for any dose of PPA. The Association commented extensively on the Horowitz study (see p. 5 of PA Comments), and now wishes to add that the study by C. A. Mitchell, referred to on page 7 of our comments, did not report comparable results with the 50 mg timed-release portion of the study. In a cross-over study, six normotensive volunteers received placebo or 50 mg PPA plus 0.25 mg belladonna alkaloids. Blood pressure and pulse were recorded every 15 minutes for the first 90 minutes and every 30 minutes for the next 90 minutes after dosing. Mitchell reported no statistically significant differences between drug and placebo on mean arterial pressure or pulse.

Nor did 11 percent of those persons who received 50 mg of PPA in a timed-release form in the Horowitz study develop "significant, sometimes severe diastolic hypertension," as CSPI asserts. (CSPI, p. 6.) Horowitz reported that four of the 37 subjects had a diastolic reading of 100 or more, and reported that one of those four participants had a maximum supine blood pressure of 145/110 mm Hg. Presumably the subject with the 145/110 mm Hg. reading had the highest diastolic reading of the four subjects with readings of 100 or more. This is not equivalent, however, to reporting that the subjects had "severe

diastolic hypertension," as CSPI states, nor did Horowitz so classify those subjects. Moreover, although Horowitz stated that three subjects in the 85 mg portion of the study received anti-hypertension therapy, he did not report that any of the subjects in the 50 mg portion of the study received anti-hypertension therapy.

CSPI further asserts that one would expect the elevated diastolic blood pressure readings reported in the subjects in the Horowitz study who received a 50 mg timed-release capsule to occur in more people if a 75 mg dose were ingested. (CSPI, p. 7.) In fact, the Noble study cited on page 7 of our comments demonstrates that no such result occurred.

The speculations of CSPI are further negated by the fact that in 1981 approximately five billion doses of PPA were taken in the form of cough/cold and weight control OTC products, with only a handful of reports of adverse reactions, which appear to be either idiosyncratic or due to overdoses.

The comments of the California Association of Neurological Surgeons, Inc. and those of Arthur F. Shinn, Pharm. D., Beecham Laboratories, raise a similar safety concern when PPA is ingested. However, the reports cited in those comments simply do not indicate that there is a relationship between PPA and the reactions reported when PPA is ingested at the dose levels recommended in the ANPR. The comments of the California Association of Neurological Surgeons, for example, report three cases of adverse reactions after ingestion of PPA. Case 1 and Case 2 are, respectively, a report of an overdose of an OTC weight-control product, and a report of ingestion of an illegal "look-alike" product. Case 3 is a report of an adverse reaction after the ingestion of an OTC "diet pill," which is not otherwise identified. As to Case 3, it should also be noted that the report states that vomiting occurred immediately after ingestion and that the adverse reaction occurred after the vomiting. It is unlikely, therefore, that the adverse reaction resulted from the ingestion of the "diet pill."

Similarly, the reports cited by Shinn involved overdoses, idiosyncratic reactions and/or illegal combinations. Case 1 involved a patient with a history of epilepsy who had a seizure apparently coincidentally with the ingestion of two combination cough/cold products. In Case 2 the patient had consumed three to five ounces of whiskey just prior to ingesting two "black capsules," each containing a combination of 200 mg caffeine, 25 mg ephedrine and 50 mg PPA, a combination which FDA has since declared to be an unapproved "new drug." (47 Fed. Reg. 35344, August 13, 1982.) Case 3 again involved two "black capsules" containing the same illegal combination.

CSPI asserts that the recommended label warning is inconspicuous and inadequate to protect persons who have hypertension, heart disease, diabetes or thyroid disease from ingesting weight control products containing PPA. (CSPI, pp. 12-13.) As an examination of the label warnings on these products shows, the warning is clear and conspicuous, as, indeed, Section 502(c) of the Act and FDA's regulations require it to be.

CSPI further asserts that "[c]onsumers have an understandable tendency to believe that drugs available on an OTC basis are safe for most potential purchases,...." (CSPI, pp. 12-13.) We believe that this is true and that it is also fully consistent with the philosophy of making medication available to the consumer on an over-the-counter basis. In stating that consumers do not read labels because they believe that OTC medicines are unqualifiedly safe for everyone, CSPI is not really questioning the safety of PPA as an OTC; it is really questioning the fundamental principle of self-medication itself -- that people are capable of using an OTC safely and effectively if they follow labeling directions.

Comments Which Assert that Phenylpropanolamine is Unsafe Because of Alleged CNS Effects

CSPI states that PPA is unsafe for use in weight control products because of reports of adverse CNS effects resulting from the ingestion of PPA. CSPI concedes that "[n]one of these incidents proves definitively that PPA can cause mental derangement," but contends that "the structural similarity is there..." between PPA and the amphetamines, adrenaline, and related sympathomimetic amines. (CSPI, p.3.) CSPI couples the structural similarity with case reports in the United States and other countries linking PPA with adverse CNS effects. CSPI cites several reports, including the Dietz survey listed in the preamble to the ANPR as Reference 9, as support for the proposition that there have been "scattered accounts that even normal doses of PPA may sometimes cause or aggravate psychotic episodes, hallucinations, or other severe behavioral aberrations that mimic amphetamine reactions." (CSPI, p.3.) We submit that the Dietz survey does not support the proposition that there are adverse CNS effects associated with the use of PPA at the dosage levels of the products currently marketed or the dosage levels proposed by the Panel. As CSPI points out, the Dietz survey is composed of scattered accounts. (CSPI, p. 3.) In addition, the seven cases referred to in the Dietz survey, which were taken from record cards of

patients in emergency rooms, are accounts of isolated cases of individual adverse reactions. There was no possibility of verification of the actual doses of PPA taken since the PPA was not taken under controlled conditions, and there was no follow-up to determine whether the symptoms reported were repeated under the same or different circumstances.

The other reports cited by CSPI (CSPI, p.3, fn. 9) also fail to support the proposition for which CSPI cites them. With regard to the Achor and Extein report of precipitation of bipolar affective disorder in three patients who had been taking diet-aid products containing PPA, one patient had been taking twice the recommended dose, and the dosage for the other two patients was not reported. Therefore, one of the cases clearly involved an overdose, and the remaining two cases may have as well. Furthermore, according to the report, all three patients had histories of mood disorders. Finally, the report did not describe the patients' psychiatric status immediately prior to taking the diet aids, or after they were withdrawn. It is therefore impossible to evaluate whether PPA played any role in the psychiatric episodes reported.

The Schaffer and Pauli report cited by CSPI involved one patient who ingested three to five pills each day from two separate bottles of diet pills. Obviously, the reaction of that patient is of no use in any evaluation of PPA.

The report by Norvenius, et al., cited by CSPI, dealt with complaints to the Swedish Adverse Drug Reaction Committee. It is unclear from the report whether the total number of complaints was 61 or 66. In any event, five patients were reported to have had psychotic episodes, but the report does not give dose levels for any of the patients. Since 48 of the patients were under age 16, it is probable that many of these patients ingested accidental overdoses. Moreover, the report specifically notes that one 17-year-old male had taken "large" quantities of a PPA and brompheniramine combination product. In view of the absence of data on the precise dosage ingested in each case, the report essentially has no probative value.

The Wharton report relied upon by CSPI describes a psychotic episode in a patient taking a cold medication containing 12.5 mg of PPA, phenyltoloxamine, phenacetin and thonzylamine. He exhibited paranoid psychosis after an eight-day period in which he had ingested 30 tablets. He was treated for the paranoid psychosis, but eight weeks after recovery he suffered a similar reaction, although he was not taking the cold medication at the time. Therefore, the psychotic reaction apparently did not result from the ingestion of PPA.

nally, CSPI cites the Kane and Greene report of three patients who took nasal decongestants containing PPA. The reaction of two of the three patients simply does not support the Center's position. One of the patients had previously been treated for undifferentiated schizophrenia. That patient's reaction may well have resulted not from the ingestion of PPA but from a preexisting mental condition. Another patient had used "two bottles" of the decongestant within one week. There is no indication as to the actual amount of PPA taken at any one time. Accordingly, once again, the report cannot be cited as support for any proposition concerning PPA.

To summarize, the five published reports discussed above include 13 patients who experienced psychotic episodes. Three of the patients were children 8 years old or younger, who probably ingested accidental overdoses, and one patient was a 17-year-old who reportedly had taken "large quantities" of a PPA and brompheniramine combination product. Among the remaining nine patients, one had taken more than the recommended dose; another may have taken more than the recommended dose (the only information available was that the patient took "two bottles"); one apparently took two PPA-containing preparations, but dosage was not specified; four had histories of affective illness or schizophrenia and one of these took more than the recommended dose; and one patient experienced another psychotic episode eight weeks after he had discontinued use of products containing PPA. Moreover, it should be reiterated that substantially all of the complaints reported by Norvenius, et al., were complaints of restlessness, irritability, etc. Furthermore, these reports primarily involved children 15 years old and younger and, therefore, most of the cases undoubtedly involved accidental ingestions or overdoses.

CSPI also cites another case in which alleged adverse CNS reactions occurred. (CSPI p. 7.) The case involved a 44-year-old woman who developed "confusion [and] grand mal seizures" approximately an hour after taking a 75 mg timed-release weight control capsule. As a careful reading of the report of the incident indicates, the woman had previously experienced grand mal seizure reactions to cough/cold medications. Therefore, her grand mal seizure reaction was idiosyncratic. There is, moreover, no established contraindication for sympathomimetic drugs for epilepsy.

Relying on Porter & Dietsch, Inc. v. Federal Trade Commission, 90 FTC 770 (1977), aff'd, 1979-2 Trade Cases ¶ 62,795 (7th Cir. 1979), CSPI asserts that PPA is unsafe because the advertising for weight control products containing PPA which does not include a health warning is misleading. (CSPI, p. 13). The

relevancy to this proceeding of the FTC's action in that case is dubious at best. In any event, CSPI misstates the scope of the ruling in Porter & Dietsch. The holding was limited to the particular advertisements at issue in that case. It was not applicable to all PPA-containing weight control products. Moreover, as FDA knows, the Panel recommended a number of label warnings for these products, as discussed above.

There is an absence of any evidence establishing that adverse CNS reactions are a side effect of the ingestion of PPA at the dosage levels proposed by the Panel. In fact, the marketing experience of cough/cold and weight control products containing PPA in the United States is support for the proposition that adverse CNS reactions are not a side effect of the ingestion of PPA. Furthermore, the marketing experience is supported by a recent double-blind, cross-over study by Seppala, reported in the British Journal of Clinical Pharmacology.¹ The Seppala study, which also included antihistamines that provided an active control, reported no euphoric effect and an improvement in perception and reaction accuracy following ingestion of PPA at a 50 mg dose level. Seppala stated in conclusion that "[i]t is noteworthy that mood elevation...was not noted after [treatment with] phenylpropanolamine." Accordingly, in view of the results of the Seppala study, the accumulated experience from the testing and marketing of cough/cold and weight control products which fails to indicate that ingestion of PPA in the doses proposed by the Panel results in adverse CNS reactions, and the fact that the cited reports of adverse CNS reactions are either reports of ingestion of doses above the recommended dosage level or are isolated incidents, we submit that no evidence has been identified that indicates that ingestion of PPA at the recommended doses is unsafe because of possible adverse CNS reactions. We believe, therefore, that further clinical testing is unnecessary in order to evaluate the safety of PPA at the dosage levels under consideration.

CSPI, citing a letter from the British Department of Health and Social Security, states that only one PPA weight control product is marketed in Britain and that the product is a prescription drug, and implies that the FDA should adopt a similar policy with respect to weight control products containing PPA. (CSPI, p. 13.) It should be noted that Britain does permit the marketing of OTC drugs containing PPA. Menley and James markets Contac, its OTC cough-cold product containing PPA, in Britain.

Comments Which Assert that PPA Is Unsafe Because it is a Drug of Abuse

CSPI and G. B. Stickler, M.D., cite drug abuse as a reason for placing PPA on prescription. (CSPI, pp. 3-5; Stickler, p.2.) CSPI relies on National Clearinghouse for Poison Control Center reports and Stickler, citing no sources, simply asserts that PPA "is the number one street-drug, at least in Minneapolis and probably in other cities in this country." (Stickler, p. 2.)

The Association has several comments on the points raised by CSPI and Dr. Stickler with respect to PPA and drug abuse.

(1) National Clearinghouse for Poison Control Centers (NCPCC) Data.

- (a) Extrapolations of NCPCC data must be made with caution since the data are derived from only 10% of the nation's poison control centers, and the 10% are not necessarily a valid sample.
- (b) The data reflect all reports of ingestions or other incidents, whether serious or not. Most of the reports discussed by CSPI with respect to PPA were made by telephone, rarely involved hospital contact and, on the average, resulted in mild, if any, side effects.
- (c) As CSPI concedes (CSPI, p.5), "a large percent of the Clearinghouse PPA cases involved children" The Association notes that this percentage is large indeed - over 40. That is, over 40% of the cases involve children under 5 years of age. Placing an ingredient on prescription to eliminate unsupervised ingestions by children is not, the Association submits, a legal or wise measure.

As FDA knows, The Proprietary Association and its members have long been active in working to reduce unsupervised ingestions of medicines by children. The Association has participated in government-sponsored conferences and various educational activities on the subject, while its members have been experimenting with, testing, improving, and using various forms of "special packaging" since 1955. Needless to say, the Association supports CSPI's attempt to reduce

accidental ingestions, including ingestions by children, of the products subject to this proposal. The Association believes, however, that attempting to combat such ingestions by placing a drug on prescription on the basis that it is "not generally recognized as safe" for OTC use is not proper.

Section 201(p) of the FDC Act defines a "new drug" as one which is "not generally recognized ...as safe and effective under the conditions prescribed, recommended, or suggested in the labeling thereof...." (Emphasis added.) In so defining the term, Congress recognized that any drug can be unsafe if used incorrectly, such as taken internally when it should be used topically and/or taken in excessive amounts. Congress therefore sought to address the question of whether a drug is safe by considering the safety of the drug in connection with the adequacy of its labeling, including its dosage recommendations, method of administration, warnings, and other precautions. Therefore, unless the labeling of the products subject to the proposal prescribes, recommends, or suggests ingestion of amounts which are toxic, such products do not meet the statutory definition of "new drug."

The Consumer Product Safety Commission (CPSC), on the other hand, has the express Congressional mandate "to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting" these and other products by requiring special packaging where appropriate. (140 U.S.C. 1472(a)(1).) Accordingly, the Association suggests that CSPI submit to CPSC what information it has on accidental ingestions of such products by children. FDA, however, is without authority to proceed against such products as "new drugs."

Nor is placing these products on prescription necessarily a useful means of protecting children from the dangers of unsupervised ingestion of drugs. Unsupervised ingestion by children is a function of the accessibility of the drug to children and the adequacy of parental supervision, not of the legal status of the drug as prescription or OTC.

- (d) The Clearinghouse data include a number of suicide gestures. The Association notes that none of the gestures succeeded. Moreover, the safety of OTCs, which are products intended to be taken according to label directions, cannot properly be judged on the basis of data regarding their use in attempted suicides.
- (e) For a general but more detailed discussion of the data contained in the August, 1981 NCPCC Bulletin, the Association is enclosing as Attachment A written comments of Charles Winick, Ph.D. Dr. Winick is a Professor at the City University of New York Graduate School, co-editor of the Journal of Substance Use and Abuse, a contributing editor of the Journal of Drug Issues and Addictive Diseases, and a longtime consultant to, and principal investigator on, many projects funded by federal government agencies concerned with drug abuse.

(3) Potential for Abuse of Phenylpropanolamine

CSPI states that the Griffith, et al., study which indicated that PPA lacks abuse potential is of questionable significance. No basis for this criticism is given. The Griffith study was well-controlled and conclusively established that drug self-administration procedures with laboratory animals have provided an important conceptual and methodological focus for the pre-clinical assessment of abuse potential. In this study, conducted at Johns Hopkins University, a quantitative ratio measure was developed which permitted comparison between the reinforcing potency of either phenylethylamine anorectics and cocaine in laboratory baboons. The well-controlled study clearly demonstrated that PPA has a zero potential for abuse.^{2/} Seppala confirmed this in humans, finding no mood-elevating component from 50 mg immediately available doses.^{1/}

(4) "Amphetamine Look-Alikes"

- (a) CSPI questions the safety of PPA for what the Center sees as the ingredient's contribution to drug abuse from the sale of "amphetamine look-alikes," described by CSPI as combinations of PPA, ephedrine, and caffeine. (CSPI, p. 3.) The Association notes that such combinations are

not Category I combinations nor is anyone, to the Association's knowledge, proposing that they be placed in Category I. They are thus not relevant to discussions of PPA when used according to the terms set forth in the ANPR. Indeed, FDA has recently taken the position that such combinations are unapproved "new drugs." (47 Fed. Reg. 35344, August 13, 1982.)

- (b) Since 1980, 43 states have considered and 33 have enacted legislation which prohibits trafficking in what CSPI describes as "amphetamine look-alikes." Both the U.S. Drug Enforcement Administration and the American Medical Association have developed model bills along this line. The Association understands that in states which have passed such legislation, the problems of abuse of such "look-alikes" has substantially declined. In addition, both FDA and the Post Office Department have instituted seizure actions against a number of manufacturers of such products.
- (c) As noted earlier, Dr. Stickler asserts that PPA "is the number one street-drug, at least in Minneapolis, and probably in other cities in this country." (Stickler, p.2.) It appears that what Dr. Stickler is discussing is not PPA in the recommended dose but rather PPA in the illegal combinations discussed above.

Comments Which Question the Effectiveness of Phenylpropanolamine

On page 1 of its comments, CSPI states that one of its concerns regarding weight control products containing PPA is the lack of evidence to support claims of efficacy. CSPI attributes this lack of evidence to the drug manufacturers' alleged refusal "to reveal to the scientific community details of most of the studies purported to back claims of efficacy." Needless to say, all studies submitted to FDA under its OTC Drug Review on PPA are public.

CSPI also states that the Panel's conclusion that the new studies presented to it (Refs. 5 through 11) established the efficacy of such products was "qualified by the statement that 'each of these studies is defective in one or more important ways'." (CSPI, p. 15.) This statement is incorrect. The Panel concluded that PPA is effective and their finding was

unanimous. What the Panel in fact stated was that:

While each of these studies is defective in one of (sic) more important facets covered by the Panel's proposed protocol, the Panel believes that the combined evidence of these studies does establish the effectiveness of phenylpropanolamine hydrochloride. (47 Fed. Reg. 8475, February 26, 1982.) (Emphasis added.)

CSPI states that the results from the 10 double-blind studies in the public docket do not "support any claim of efficacy." (CSPI, p. 19.) To the contrary, the following data represents the weight loss achieved by patients on phenylpropanolamine and patients on placebo in eight clinical studies presented to the Panel:

Average Weight Loss Per Week

Phenylpropanolamine	1.16 lbs.
<u>Placebo</u>	<u>.56 lbs.</u>

The difference is .60 lbs.

Moreover, several years ago FDA evaluated 210 double-blind studies in which prescription appetite suppressant products were compared against placebo. These studies represented 105 new drug applications and contained data on nearly 10,000 patients. Scoville^{3/}, in reporting on these results, indicated that of the 4,543 patients on active drug and 3,100 patients on placebo, the weight loss averaged 0.56 pounds per week more for each patient on active drug than on placebo. The results with OTC products containing PPA compare favorably with this result. The average weight loss achieved by patients on the phenylpropanolamine program was .60 pounds more than the weight loss achieved by the patients on the placebo-plus-diet program. It is also important to point out that, when phenylpropanolamine was evaluated in these double-blind clinical studies against either a lactose capsule or an active prescription medication, each patient was given, in addition to medication, a 1250 calorie diet, as well as explicit directions from a physician. In other words, in each case the "placebo" was associated with a diet designed to cause loss of weight under the direction of a physician. Therefore, the amount of weight loss achieved by patients on the phenylpropanolamine program was even more significant because the PPA was being compared with another active program, that is, reduced diet and medical directions as well as placebo.

In conclusion, we submit that the cited studies are sufficient to support the efficacy claim made by the various manufacturers, as the Panel concluded.

CSPI cites the FTC decision in the Porter & Dietsch case, discussed above, as if it were a finding on the ineffectiveness of PPA for weight loss. (CSPI, p. 14.) Again, this misstates the case. The question put at issue by the complaint in Porter & Dietsch was "not whether the claims of weight loss are false but instead whether at the time they were made [Porter & Dietsch] possessed reasonable substantiation for them." Porter & Dietsch, Inc., 1976-1979 CCH FTC Complaints and Orders ¶ 21,320 at 21,329. The Commission made no finding as to the efficacy of PPA as an anorectic. Porter & Dietsch, supra at 21,331.

CSPI also asserts that weight control products containing PPA are of no long term benefit because users may regain weight when use is discontinued. OTC weight control products containing PPA are appetite-suppressants which are marketed as an adjunct to assist the motivated consumer on a diet. The products are marketed with diets that are based on a reduction in caloric intake, and the labelling states that weight control will occur only if the product is taken while caloric intake is reduced. Nor do these products claim that weight will not be regained if the person's caloric intake is increased.

Moreover, there is evidence which contradicts CSPI's assertion. Dr. Stanley Shachter, Professor of Psychology at Columbia University, recently concluded a long-term study to determine whether overweight patients continue to maintain reduced weight after a successful weight-loss program.⁴⁷ Asked about their weight histories, of 40 people who were obese at the outset, 25 reported losing at least 10 percent of their weight (an average of 34.7 pounds) and therefore becoming no longer obese (that is, within 10 percent of the average weight for their height and age), and remaining at that weight for an average of 11.2 years.

CSPI also cites the statement in the American Medical Association's AMA Drug Evaluations that OTC products containing PPA are "only minimally effective." (CSPI, pp. 14-15.) This characterization has been repeated verbatim year after year, but investigation of the AMA's sources reveals that no scientific studies or proof of any sort are cited by the AMA to support this description of PPA.

Comments Which Question the Validity of the Silverman Study Cited by the Agency and by The Proprietary Association

In its critique of the Silverman study,^{5/} cited in the Agency's preamble and in CSPI, CSPI states that "the experimental design is flawed in so many important ways that one could have predicted in advance that no effects would be seen." (CSPI, p.9.) When analyzed, this criticism amounts to three points: that the study groups were too small and included only normal, healthy volunteers; that blood pressure values were presented as means for each subgroup, rather than individually; and that only one of the three subgroups was double-blinded. Having consulted with Dr. Silverman, the principal investigator for the cited study, the Association believes that these criticisms of the study are entirely without merit. The so-called "flaws" were all the result of a study design explicitly established in accordance with accepted clinical procedures to eliminate investigator or other bias.

Thus, the pool of 37 volunteers who received active medication was divided into three smaller subgroups at separate sites with a separate group of qualified investigators, each conducting its study independently of the other two subgroups. The total number of volunteers who received active medication was actually the same as the number of volunteers who received active medication (in an overdose of 85 mg) in one of the Horowitz studies on which CSPI relies so heavily. In fact, CSPI characterizes that Horowitz study as "large." (CSPI, p. 6.) Similarly, the fact that the volunteers were normal, healthy adults was in accordance with accepted practice and was also true of both of the Horowitz studies.

The use of group means to report blood pressures is an acceptable biostatistical procedure.^{6/}

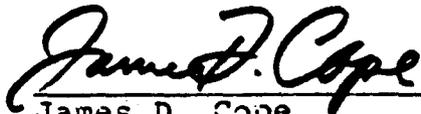
Finally, the fact that only one of the three subgroups was double-blinded is also not a "flaw" in the study. Each of the three subgroups was treated differently on this score for sound reasons. Study of one subgroup was open in order to simulate the conditions in the actual over-the-counter consumer use of the product. The study of a second group was single-blinded and the study of the third subgroup was double-blinded. The fact that all three subgroups studied under these various conditions produced no significant blood pressure effects reinforces the conclusion that at the tested dosage level, 25 mg, which is the most commonly-marketed immediate release dosage level, phenylpropanolamine produces no adverse blood pressure effects.

In conclusion, it should be noted that the Silverman study is only one of some 60 controlled clinical studies, cited by the Association in its comments, which demonstrate that phenylpropanolamine does not induce hypertension. This mass of positive data, together with almost 50 years of safe use of PPA in this country, clearly outweighs the handful of adverse reports referred to in the CSPI and other comments.

The Association appreciates the opportunity to submit these reply comments.

Sincerely,

THE PROPRIETARY ASSOCIATION

A handwritten signature in cursive script that reads "James D. Cope". The signature is written in black ink and is positioned above a horizontal line.

James D. Cope
President

FOOTNOTES

- 1/ Seppala, et al., British Journal of Clinical Pharmacology, 12: 179-188, 1981.
- 2/ Griffith, et al., Biological Psychiatry, 13:1383, 1978.
- 3/ Scoville, B.A., "Review of amphetamine-like drugs by the Food and Drug Administration," Obesity in Perspective, Fogarty International Center Series on Preventive Medicine, Vol. II (Bray, G.A., ed.), U.S. Government Printing Office, Washington, D. C., 1975, pp. 441-443.
- 4/ "Don't Sell Habit Breakers Short," Psychology Today, August, 1982.
- 5/ Current Therapeutic Research, 28: 185-194, 1980.
- 6/ Goldstine, A., Biostatistics, MacMillan, N.Y., 1968, p. 272.

SOME COMMENTS ON POISON CONTROL CENTER REPORT ON PHENYLPROPANOLAMINE

August 1981

Charles Winick, Ph.D.

1. The August, 1981 Bulletin of the National Clearinghouse for Poison Control Centers carried an article on phenylpropanolamine Weight Control Products.

For the calendar year 1979, there were a total of 144,262 reports of all substances. Of these, 739 were diet aids, of which 328 were named phenylpropanolamine products, or about $\frac{1}{4}$ of 1% of the total. I obtained this breakdown from several conversations which I had with the senior author of the Poison Control Center report.

2. As someone who has worked for years in the epidemiology of substance abuse, on behalf of the National Institute of Drug Abuse and other agencies, I believe that the tone of the Poison Control Center report on phenylpropanolamine is unduly and inappropriately pessimistic. I do not believe that a valid extrapolation can be made from the actual data to the report's estimate of 10,000 phenylpropanolamine problem cases nationally.
3. The cases reported to the Poison Control Center may or may not be representative of what is actually happening nationally. For example, the country's largest Poison Control Center, in New York City, is one of the 90% of the country's Centers not reporting its experience to the national office. The 10% of the Centers reporting may not represent a valid sample of the national situation.
4. Of the 328 cases with product names, 64% involved no symptoms of any kind and the majority of the remainder did not have significant symptoms. Overall, most cases were telephone-informational communications. Only 6% involved a hospital contact. On the Poison Control Center scale from mild(1) to moderate(2) to severe(3), the phenylpropanolamine reports were, overall, mild(1.4).
5. Over two fifths of the phenylpropanolamine reports were under 5 years of age and almost one third were between 14 and 18 years of age. The former are presumed to be accidental and the latter may have been seeking a "high". If so, they would be disappointed because phenylpropanolamine is not an effective stimulant. The number of accidental cases is another reflection of the importance of the parent's role in management of medications in the home by always keeping medications unavailable to children.

There were about 200 suicide gestures or attempts. Not only did none of these succeed but there was no fatality in the entire year from phenylpropanolamine, for any reason.

SOME COMMENTS ON POISON CONTROL CENTER REPORT ON PHENYLPROPANOLAMINE

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6. The report does not consider the temporary breakout or peaking noted by many epidemiologists when a substance first is employed by larger numbers of people. Because of unfamiliarity with the substance and a barrage of media publicity, when a substance first becomes widely used, there is often a sharp increase in emergency room visits, and calls, reports to poison control centers, mostly for reassurance. After a year or two, the number of such visits and reports declines. It may well be, therefore, that the 1979 reports of phenylpropanolamine incidents represent a temporary cresting which will diminish in the near future.
7. A substantial contributor to reports of problems with phenylpropanolamine is the proliferation of "look-alike" products which may include phenylpropanolamine along with other drugs. I understand that in every state which has enforced restrictions against "look-alike" drugs, there has been a uniform decline in reports of problems with phenylpropanolamine. If the state of Washington bans "look-alikes", this ban, in combination with the cresting phenomenon noted in the preceding paragraph, should lead to a sharp decline in reports of phenylpropanolamine mentions to Poison Control Centers.

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