Appendix C

Consumer Healthcare Products Association

Appendix C

Joint Statement
On
The Safety of Phenylpropanolamine (PPA)
As An Ingredient In Over-the-Counter (OTC) Medications

Nonprescription Drug Manufacturers Association of Canada
and
The Proprietary Association

May, 1989

INDEX OF TABLES AND FIGURES

JOINT STATEMENT
ON
THE SAFETY OF PHENYLPROPANOLAMINE (PPA)
AS AN INGREDIENT IN OVER-THE-COUNTER (OTC) MEDICATIONS

I.   EXECUTIVE SUMMARY

A.   Summary Statement

In depth review of published and unpublished clinical data on the
use of phenylpropanolamine (PPA) in over-the-counter (OTC) medi-
cines demonstrates that this ingredient is a safe and effective
nasal decongestant and appetite suppressant.

This Statement critically reviews these data and supports the
continued OTC availability of phenylpropanolamine.

The compound of interest in Canada and the United States is the
racemic mixture d, 1 norephedrine (Phenylpropanolamine, USP), which
differs from all other isomers and racemates of norephedrine. In
this Statement the abbreviation, PPA, of the name phenylpropanola-
mine, is used to designate d, 1-norephedrine, the racemic mixture
of two stereoisomers d-norephedrine and 1-norephedrine.

B.   Summary Conclusions

1.   a.   A substantial number of clinical (1, 2, 3, 4, 5, 6, 7,
          8, 9, 10, 11, 13, 14, 15, 16, 17, 19, 20, 21) and
          epidemiologic (12) studies demonstrate that clinically-
          recommended doses of PPA produce no clinically signifi-
          cant changes in blood pressure, heart rate or EKG.
          Safety has been demonstrated in acute and longer term,
          repeated-dose studies in healthy volunteers and over-
          weight, hypertensive patients. (See Section II.)

     b.   Since the confusion regarding the vasoactive potential
          of phenylpropanolamine that arose from the Horowitz
          studies (Section IV.B.), one "tachyphylactic" and two

b.   (continued)

"rising dose titration" studies were sponsored by
SmithKline Consumer Products and CIBA Consumer
Pharmaceuticals to further elucidate the dose-response
relationship between PPA and blood pressure. Each of
these studies provides further support for the
conclusion that PPA in OTC recommended doses is safe.
(See Section III.)

2.   Isomers chemically related to PPA have different
pharmacological effects and their presence in products
labeled as containing PPA has unjustly tainted PPA's
otherwise good record of safety. (See Section IV.A.)

3.   Furthermore, PPA as a single ingredient is not an euphoriant
and is not and never has been a recreational drug of abuse.
This conclusion is based on both animal and human studies and
includes reports of the Drug Abuse Warning Network (DAWN) and
the National Network of Poison Control Centers. (See Section
V.)

4.   Analysis of reports of adverse reactions to PPA from the
published literature and FDA's Spontaneous Reporting System
shows that the risk of serious adverse reactions associated
with the use of PPA alone is extremely small and well within
the margin of safety of other generally recognized safe and
effective OTC ingredients. (See Section V.)

II. PUBLISHED STUDIES DEMONSTRATE THAT CLINICALLY RECOMMENDED DOSES OF PPA PRODUCE NO CLINICALLY SIGNIFICANT CHANGES IN BLOOD PRESSURE, HEART RATE OR EKG

A. **Summary**

Despite observations that under specialized experimental conditions in the clinic or animal laboratory PPA can be shown to elevate blood pressure, PPA's safety re potential cardiovascular effects at expected OTC exposure levels has been demonstrated in acute and longer term repeated-dose studies -- including studies in normotensive obese and nonobese persons, controlled mildly hypertensive obese patients, controlled hypertensive patients and other special patient populations.

B. **Introduction: Dosage Forms**

PPA is available in Canada and the United States as an OTC nasal decongestant in daily doses of up to 150 mg (25 to 37.5 mg every 4 hours) and in the United States as an OTC appetite suppressant in immediate-release doses of 25 mg t.i.d. and once-daily controlled-release doses of 75 mg. Table A (page 3a and b) contains a representative listing of PPA containing OTC products in Canada and the United States.

C. **"Meaningful Increases" In Blood Pressure**

As stated by Reidenberg (22), "any hypertensive response to PPA should be evaluated in the context of moment-to-moment fluctuations in blood pressure seen in individuals who have their blood pressure measured repeatedly." Reidenberg based his conclusion on the work of Pickering et al. (23) and Harshfield et al. (24). Reidenberg (22) states:

Phenylpropanolamine

Head & Chest Cold Medicine
(Richardson-Vicks Health Care)
p 420, 649

Phenylpropanolamine Bitartrate

Alka-Seltzer Plus Cold Medicine (Miles
Inc.) p 413, 608
Alka-Seltzer Plus Night-Time Cold
Medicine (Miles Inc.) p 413, 608

Phenylpropanolamine Hydrochloride

A.R.M. Allergy Relief Medicine Caplets
(SmithKline Consumer Products)
p 427, 694
Acutrim Late Day Appetite Suppressant
(CIBA Consumer) p 406, 536
Acutrim 16 Hour Appetite Suppressant
(CIBA Consumer) p 406, 536
Acutrim II Maximum Strength Appetite
Suppressant (CIBA Consumer) p 406,
536
Allerest Headache Strength Tablets
(Pharmacraft-Pennwalt) p 635
Allerest Sinus Pain Formula
(Pharmacraft-Pennwalt) p 418, 635
Allerest Tablets (Pharmacraft-Pennwalt)
p 418, 635
Allerest 12 Hour Caplets
(Pharmacraft-Pennwalt) p 635
Bayer Children's Cold Tablets
(Glenbrook) p 407, 544
Bayer Children's Cough Syrup
(Glenbrook) p 407, 544
Cheracol Plus Head Cold/Cough
Formula (Upjohn) p 430, 715
Chexit Tablets (Sandoz Consumer)
p 678
Comtrex Multi-Symptom Cold Reliever
Tablets/Caplets/Liquid
(Bristol-Myers) p 404, 525
Congespirin For Children Aspirin Free
Liquid Cold Medicine (Bristol-Myers)
p 404, 527
Contac Caplets (SmithKline Consumer
Products) p 427, 695
Contac Capsules (SmithKline Consumer
Products) p 427, 696
Contac Severe Cold Formula Caplets
(SmithKline Consumer Products)
p 427, 696
Coricidin 'D' Decongestant Tablets
(Schering) p 426, 687
Coricidin Demilets Tablets for Children
(Schering) p 426, 688
Coricidin Extra Strength Sinus
Headache Tablets (Schering) p 688
Demazin Nasal Decongestant/
Antihistamine Repetabs Tablets &
Syrup (Schering) p 426, 689
Dexatrim Capsules (Thompson Medical)
p 713
Caffeine-Free Dexatrim Maximum
Strength Capsules (Thompson
Medical) p 713
Dexatrim Maximum Strength Capsules
Plus Vitamin C (Thompson Medical)
p 430, 713

Caffeine-Free Dexatrim Maximum
Strength Caplets (Thompson Medical)
p 430, 713
Dexatrim Maximum Strength Plus
Vitamin C Caplets (Thompson
Medical) p 430, 713
Dexatrim Maximum Strength Pre-Meal
Caplets (Thompson Medical) p 430,
713
Dimetapp Elixir (Robins) p 422, 660
Dimetapp Extentabs (Robins) p 422,
660
Dimetapp Plus Caplets (Robins) p 422,
660
Dimetapp Tablets (Robins) p 422, 660
4-Way Cold Tablets (Bristol-Myers)
p 404, 528
Naldecon CX Adult Liquid (Bristol)
p 521
Naldecon DX Adult Liquid (Bristol)
p 522
Naldecon DX Children's Syrup (Bristol)
p 522
Naldecon DX Pediatric Drops (Bristol)
p 522
Naldecon EX Children's Syrup (Bristol)
p 523
Naldecon EX Pediatric Drops (Bristol)
p 523
Pyrroxate Capsules (Upjohn) p 431,
716
Robitussin-CF (Robins) p 422, 661
St. Joseph Cold Tablets for Children
(Plough) p 640
Sinarest Regular & Extra Strength
Tablets (Pharmacraft-Pennwalt)
p 637
Sine-Off Sinus Medicine Tablets-Aspirin
Formula (SmithKline Consumer
Products) p 428, 702
Sucrets - Cold Decongestant Formula
(Beecham Products) p 515
Triaminic Allergy Tablets (Sandoz
Consumer) p 681
Triaminic Chewables (Sandoz
Consumer) p 681
Triaminic Cold Syrup (Sandoz
Consumer) p 425, 681
Triaminic Cold Tablets (Sandoz
Consumer) p 425, 681
Triaminic Expectorant (Sandoz
Consumer) p 425, 682
Triaminic-DM Cough Formula (Sandoz
Consumer) p 425, 682
Triaminic-12 Tablets (Sandoz
Consumer) p 425, 682
Triaminicin Tablets (Sandoz Consumer)
p 425, 683
Triaminicol Multi-Symptom Cold Syrup
(Sandoz Consumer) p 425, 683
Triaminicol Multi-Symptom Cold Tablets
(Sandoz Consumer) p 425, 683
Trind (Mead Johnson Nutritionals)
p 601
Trind-DM (Mead Johnson Nutritionals)
p 602
Tussagesic Tablets (Sandoz Consumer)
p 684

TABLE A: LISTING OF PPA PRODUCTS IN CANADA

Cold + Decongestant Capsules

Contac Prepartions

Coricidin "D"

Corsym

Dimetapp Oral Infant Drops

Dristan

Dristan Long Lasting Capsules

Entex LA

Ornade

Ornade-A.F.

Ornade-DM

Ornade Expectorant

Pharmetapp

Pharminieol

Robintussin-CF

Sine-Off Preparations

Sinutab SA

Tuss-Ornade

Vicks Formula 44D

Source: Provided by the Nonprescription Drug Manufacturers
Association of Canada, November, 1988

"These fluctuations in blood pressure have been studied extensively by Pickering et al. (1982) and Harshfield et al. (1984). They measured blood pressure every 15 minutes for 24 hours with an automated device while normal and hypertensive subjects went about their ordinary activities. They found that, in normal subjects, the daily range between the highest and lowest diastolic blood pressure measurements in any one individual averaged 46 ± 11 mm Hg. The maximum systolic pressure achieved by a normotensive subject averaged 90 mm Hg higher than the lowest systolic pressure measured in that subject during the 24-hour period. These examples should indicate to those not familiar with the subject how much moment-to-moment variation in blood pressure normally exists. It should be considered, therefore, whether the blood pressure response to specific doses of phenylpropanolamine raises an individual's blood pressure above the levels that occur in response to exercise, anxiety, or fear."
(Reference 22 at page 274; emphasis supplied)

Admittedly, "meaningful increases" in blood pressure have been defined a variety of ways in the literature. However, pertinent in this regard are the observations noted above, of Pickering et al. (23) and Harshfield et al. (24) that the normal 24 hour range of blood pressure variation is on the order of 46 mm Hg and 90 mm Hg between the highest and lowest diastolic and systolic blood pressures, respectively. In this context, the relatively . conservative definition by Weintraub et al. (1) used in studying mildly obese women on PPA therapy seems reasonable. That is, "meaningful increases" in blood pressure are a diastolic blood pressure >100 mm Hg, or a 10 mm Hg increase in diastolic blood pressure, a systolic blood pressure >150 mm Hg, or a 20 mm Hg increase in systolic blood pressure.

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D. Pivotal Studies Demonstrating The Safety Of PPA In Normotensive Individuals

A number of important recent studies have demonstrated the safety of PPA in normotensive obese and nonobese individuals — and in hypertensives (as discussed in Section II.E. below). While small, but statistically significant, increases in diastolic and systolic blood pressure have been observed in some of these studies, these changes in blood pressure are not clinically significant at OTC recommended doses and certainly do not represent any "meaningful increases" as defined (above) by Weintraub et al. (1).

All of these investigators (1-11) — studying 1,684 normotensive individuals on a variety of single and multiple dose regimens of PPA — conclude PPA is a safe OTC ingredient and does not cause meaningful increases in blood pressure nor changes in heart rate or EKG at recommended OTC doses. An epidemiologic study utilizing a patient population from the Puget Sound databases (12) on 253,334 filled PPA prescriptions also supports this conclusion.

Table B (pages 5a, b,c) provides a tabular summary of the key findings supporting this conclusion, and brief descriptions of the pivotal studies follow. Copies of these study reports are found in the Appendix.

1. Blackburn et al.: Determinates of the pressor effect of PPA in healthy subjects. (Supported by PHS grants 1R01 HL-31989 and The Thompson Medical Company, First European Congress on Obesity, Stockholm, Sweden, June 5-6, 1988; and North American Association for the Study of Obesity Meeting, Banff, Canada, August 25-28, 1988; Reference 5)

    Blackburn et al. (2) conducted a multi-center, randomized, double blind, single-day clinical trial among 881 individuals

TABLE B

SUMMARY TABLE OF KEY FINDINGS
FROM PIVOTAL STUDIES ON NORMOTENSIVE SUBJECTS

Dose Regimen	Total Study n	Baseline	Key Findings
Blackburn et al. (Reference 2)			
<u>Single and Multiple Dose/One Day</u> 75 mg SR 25 mg IR tid Placebo	881	normotensive obese/nonobese	No meaningful increases in BP; Magnitude of pressor effect of PPA depends on baseline intrinsic sympathomimetic activity
Pugliese (Reference 3)			
<u>Multiple dose/30 d</u> 50 mg PPA qid 50 mg PPA + 650 ASA placebo	68	normotensive nonobese	No significant differences among groups in vital signs or in clinical lab test results
Weintraub et al. (Reference 1)			
<u>Multiple dose</u> 75 mg SR/12 weeks placebo	106	normotensive obese	Three subjects on placebo and three subjects on PPA showed meaningful blood pressure increases of comparable magnitude; no changes in ECG
Renvall and Lindqvist (Reference 4)			
<u>Multiple dose</u> 50 mg IR bid/3 days 100 mg IR bid/3 days	70	normotensive nonobese	No elevation in blood pressure in subjects on PPA No CNS stimulation
Noble, R. (Reference 5)			
<u>Single dose/1 day</u> 75 mg SR PPA 200 mg caffeine 75 mg SR PPA plus 200 mg caffeine placebo	288	normotensive obese/nonobese	No significant cardiovascular (blood pressure and pulse) or subjective effects due to PPA Statistically significant but clinically insignificant increases with caffeine alone or in combination with PPA in supine and standing diastolic blood pressure (relative to baseline)

TABLE B (continued)

Dose Regimen	Total Study n	Baseline	Key Findings
Liebson, I., et al. (Reference 6)			
Single & Multiple Dose/1 Day 75 mg SR/one dose 25 mg IR tid placebo	150	normotensive nonobese	No clinically and few statistically significant effects due to drug treatment on standing, sitting and supine blood pressure and heart rate No euphorogenic or "amphetamine like" effects were noted
Mitchell (Reference 7)			
Multiple dose 50 mg SR bid/5 days; 50 mg PPA plus 0.25 belladonna alkaloids SR placebo	32	normotensive nonobese	No significant changes in mean arterial blood pressure due to PPA
Single dose 100 mg PPA plus 0.50 belladonna alkaloids SR placebo	6	normotensive nonobese	No significant changes in mean arterial blood pressure due to PPA
Goodman et al. (Reference 8)			
Multiple dose 75 mg SR/7 days placebo	18	normotensive nonobese	No evidence of effects of PPA on blood pressure, heart rate, or diurnal variations in blood pressure or heart rate
Lake et al. (Reference 9)			
Multiple dose 75 mg SR/14 days placebo	14	normotensive nonobese	No clinically significant increases in blood pressure and no substantial changes in catecholamine levels
Saltzman et al. (Reference 10)			
Multiple dose 25 mg IR tid/4 days 75 mg SR	14	normotensive	No evidence of elevated blood pressure in subjects on PPA No clinically significant changes in laboratory tests

TABLE B (continued)

Dose Regimen	Total Study n	Baseline	Key Findings

Silverman, H. I., et al. (Reference 11)

| Single dose/ 1 Day 25 mg IR 25 mg IR plus 100 mg caffeine placebo | 37 | normotensive nonobese | No statistical difference in either systolic or diastolic blood pressures with respect to test preparation based on baseline values throughout the study |

Aselton, P., and H. Jick (Reference 12)

| Epidemiologic | 253,334 filled prescrip- tions | hospitalized, Puget Sound Database | "The risk of hospitalization for the disorders studied attri- butable to taking PPA contain- ing cough and cold remedies . . . if present at all . . . is very small." |

Note: IR = Immediate Release
       SR = Sustained Release
       ASA = Aspirin
       PPA = Phenylpropanolamine

in four categories of body weight (ranging from normal to extremely obese) to determine the pressor effect of oral PPA. Doses compared were one dose of 75 mg PPA sustained release (SR), 25 mg PPA immediate release (IR) t.i.d., and matching placebo capsules t.i.d. The 75 mg SR capsules of PPA were followed by two doses of placebo capsules; doses were given at 8:00 am, noon, and 4 pm. Thus, all three test groups received one of the three dosage forms at each of the times indicated, each dose being given with a full glass of water. Supine and standing systolic and diastolic blood pressure and pulse were measured eleven times during a 12-hour session. The median age of the study population was 28 years, 56% were females, 73% were Caucasian, and 47% were in excess of 30% above their ideal body weight. A statistically significant, but clinically insignificant, pressor effect for short-term administration of PPA was observed. Using a linear model, Blackburn et al. identified three independent factors (baseline diastolic blood pressure and, to a lesser extent, baseline body weight and treatment) that explained the peak elevation in blood pressure. This effect was smaller for the three divided-dose formulation and generally occurred in the first six hours after initial drug administration. Differences in blood pressure response to PPA were less in the standing than supine position. These results suggest that the magnitude of the pressure effect of PPA depends upon baseline intrinsic sympathetic activity.

Blackburn et al. (2) concluded:

> "Our study has demonstrated a definite effect of PPA on diastolic blood pressure, the magnitude of which, however, is clinically insignificant (less than 4 mm Hg). The averaged difference in peak standing diastolic pressure between subjects in the SR formulation and the placebo group was 1.0 mm Hg, and the difference between the IR formulation and the placebo group was 0.5 mm Hg. The corresponding differences in peak supine

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diastolic pressure were 2.8 mm Hg and 1.6 mm
Hg for the two formulations, respectively.
Only in a study population such as in the
current trial (881 patients) could this
minimal effect of PPA be reliably demon-
strated. Furthermore, it is noted that
short-term administration of PPA in healthy,
normotensive obese and lean individuals is
rarely associated with a peak diastolic
pressure above 90 mm Hg and peak elevation
[greater than 90 mm Hg] occurred no more
often than in placebo subjects.

"Baseline diastolic blood pressure, body
weight, and intrinsic autonomic activity were
found to be important determinants of blood
pressure response to short-term administra-
tion of PPA in healthy Americans.

"In our study, the pressor response to the
sympathomimetic agent PPA is shown to be
related inversely to the degree of obesity.
We have also noted that this pressor effect
is less in subjects with higher baseline dia-
stolic pressure and in the standing versus
supine position. These observations,
together with Biaggioni's finding [Reference
18, this volume] of direct relationship
between the severity of the orthostatic
hypotension and the magnitude of blood
pressure elevation to PPA (Biaggioni et al.,
1987), are consistent with the interpretation
that the pressor effect of sympathomimetic
agent such as PPA complements autonomic
nervous activity.

"We believe that our study supports the
safety of PPA as an OTC remedy. Further,
those subjects whose safety was most feared
for, the obese, those with slightly elevated
BP, or any augmented intrinsic sympathetic
tone may have an equal or even greater safety
margin." (Reference 2)

In summary, Blackburn et al. (2) concluded that their
"results suggest that the magnitude of the pressure effect of
PPA depends upon baseline intrinsic sympathomimetic activity"
and that the magnitude of the PPA effect on diastolic blood

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pressure "is clinically insignificant (less than 4 mm Hg)."
A full description of the Blackburn et al. study is found in
Reference 2 of the Appendix.

2. Pugliese, P.T.: Sine-Aid II. Human safety study. Federal
    Register. Establishment of a Monograph for OTC cold, cough,
    allergy, bronchodilator and antiasthmatic drug products.
    Docket No. 76N-0052 (1976) (Reference 3)

The lack of adverse cardiovascular reactions to PPA was
confirmed by Pugliese (3) in a 30-day safety study designed
to evaluate potential drug interactions between PPA and
aspirin. The total daily dose of PPA used in this study was
200 mg, higher than the recommended maximum daily dose of
PPA.

Pugliese used a randomized, placebo-controlled design to
assign adult volunteers (65 males and 3 females) to one of
four treatment groups. The treatments were 50 mg PPA , 50 mg
PPA plus 650 mg aspirin, 650 mg aspirin alone, and placebo.
The volunteers took these doses four times daily for up to 30
days. Vital signs were measured and clinical observations
were made the day before starting treatment and after 7, 15,
22, and 30 days of treatment; laboratory tests were conducted
at baseline, at the end of treatment, and 1 week after the
end of treatment. Fifteen volunteers withdrew from the study
for various reasons, none because of adverse reactions.

There were no significant differences among the groups in
vital signs or clinical laboratory test results. These high
doses of PPA (200 mg per day for 30 days), with and without
aspirin, produced no significant elevation of blood pressure
or pulse rate compared to placebo treatment.

A full presentation of clinical information from the study is
presented in Reference 3 of the Appendix.

3.   <u>Weintraub, M., et al.: Phenylpropanolamine OROS (Acutrim)</u>
<u>vs. placebo in combination with caloric restriction and</u>
<u>physician-managed behavior modification. Clin. Pharmacol.</u>
<u>Ther. 39:501-9, 1986 (Reference 1)</u>

<u>Weintraub et al.</u> (1) studied the effects of a sustained
released SR formulation of PPA vs. placebo in combination
with physician-managed behavior modification, mild caloric
restriction, and exercise weight control program in 106
healthy, overweight women in a 14-week double-blind clinical
trial. In addition to concluding that the sustained release
PPA formulation under study "was a safe and modestly
effective adjunct to a weight control program" (page 507 of
reference 1), Weintraub et al. (1) also concluded the
following with respect to blood pressure and pulse:

> "For all participants up to the time of
> leaving the study, there were slight
> decreases in sitting mean blood pressure in
> both groups (Acutrim, 116/74 to 112/73 mm Hg;
> placebo, 115/74 to 112/73 mm Hg). There was
> a slight increase in pulse at week 14 in the
> placebo group (74 to 77 bpm) and at some time
> points in the Acutrim group (maximum heart
> rate at week 12 was 79 bpm vs. 75 bpm at week
> 2). Examination of individual participants'
> blood pressures without knowledge of treat-
> ment assignment revealed that seven partici-
> pants in each group had some increase. The
> criteria for a 'clinically meaningful' blood
> pressure increase were: diastolic pressure >
> 100 mm Hg; systolic pressure > 150 mm Hg; or
> a 20 mm Hg increase in systolic or 10 mm Hg
> increase in diastolic pressure even if still
> within normal limits. <u>Three participants in</u>
> <u>the placebo group met the criteria (104/70 to</u>
> <u>120/80, 138/84 to 154/92, and 98/58 to 104/78</u>
> <u>mm Hg). Similarly, three women taking</u>
> <u>Acutrim had meaningful increases (100/70 to</u>
> <u>130/84, 120/82 to 135/86, and 110/66 to</u>
> <u>120/88 mm Hg).</u> Two of these latter partici-
> pants left the study, but neither one because
> of adverse drug reactions (lost to follow up
> and 'personal reasons').

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"ECGs were obtained at entry and upon leaving
the study. No participants had any change
from her initially normal ECG." (Page 505-6
of Reference 1; emphasis supplied.)

4. Renvall, U., and N. Lindqvist: A double-blind clinical study
   with Monhydrin tablets in patients with non-allergic chronic
   rhinitis. J. Int. Med. 7: 235-239, 1979 (Reference 4)

   In a double-blind, controlled clinical trial of the efficacy
   of PPA for treatment of rhinitis, relatively high doses of
   PPA (50 or 100 mg twice daily) produced no adverse reactions,
   including no elevation of blood pressure and no CNS
   stimulation (4).

   This was a double-blind clinical trial in 70 patients with
   non-allergic rhinitis. The patients were divided into groups
   receiving 50 mg or 100 mg PPA or placebo twice daily for 3
   days. The higher dose of PPA (100 mg) was significantly more
   active than 50 mg PPA or placebo in causing reduction in the
   symptoms of rhinitis. No side-effects were noted; there was
   no evidence of CNS stimulation and no elevation of blood
   pressure in the groups given either dose of PPA. [Monohydrin
   tablets contain PPA; please note that other ingredients could
   not be identified.]

5. Noble, R.: A controlled clinical trial with the
   cardiovascular and psychological effects of
   phenylpropanolamine and caffeine. Drug Intell. Clin. Pharm.
   22: 296-299, 1988 (Reference 5)

   In a large study of healthy normotensive volunteers Noble (5)
   concluded that PPA had no clinically significant effects on
   blood pressure, pulse and subjective effects.

Noble (5) evaluated the cardiovascular and psychological effects of PPA and caffeine in a large controlled clinical investigation of 288 healthy normotensive volunteers representing a range of weight categories from normal to extremely obese.

Subjects were randomly assigned to one of four drug treatment groups: PPA 75 mg sustained release (SR), caffeine 200 mg, PPA SR 75 mg plus caffeine 200 mg, or placebo. Study medication was administered as a single dose following double-blind procedures. Blood pressure (standing and supine) and pulse were measured nine times during a twelve-hour experimental session.

As stated by Noble (5):

> "Data analysis indicated no significant
> cardiovascular or subjective effects due to
> PPA. Caffeine, however, was associated with
> statistically reliable though clinically
> insignificant changes from baseline diastolic
> blood pressure in both supine and standing
> positions. The rank order of the change
> indicated larger increases for the subjects
> who received caffeine, either alone or in
> combination with PPA, as compared with those
> who received PPA alone or placebo. No
> statistically significant differences between
> PPA and placebo were observed. Subjects in
> the heavier weight categories had higher
> blood pressure levels throughout the session
> as compared with those of normal weight.
> There was no difference among the study
> groups in subjective effects. These results
> provide evidence supporting the safety of
> currently recommended doses of sustained-re-
> lease PPA, either alone or in combination
> with small doses of caffeine in healthy
> individuals." (Reference 5)

See Reference 5 for a full discussion of study results including Figures 1, 2, and 3 regarding blood pressure

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fluctuations over the course of the study, heart rate changes
over the course of the study, and peak change from baseline
in standing diastolic blood pressure.

6.   Liebson, I. et al.: Phenylpropanolamine: effects on
     subjective and cardiovascular variables at recommended
     over-the-counter dose levels. Supported in part by NIDA
     Grants DA03889 and DA00050 and The Thompson Medical Company;
     J. Clin. Pharmacol. 27: 685-693, 1987. (Reference 6)

Liebson et al. (6) conducted two clinical studies to evaluate
the effects of PPA on measures of blood pressure, pulse and
subjective state (mood). They concluded that analysis of
pulse and blood pressure variables revealed no significant
effects for drug treatment conditions.

One-hundred-fifty subjects participated in a parallel groups
design that compared 75 mg sustained-release (SR) preparation
with a 25 mg t.i.d. dosing regimen and placebo. Fifty-nine
of these subjects participated in an additional crossover
component that compared SR PPA 75 mg with placebo. Measures
of blood pressure, pulse and subjective drug effect were
obtained nine times through the course of a 12-hour session.

Analysis of pulse and blood pressure readings obtained in
standing, sitting and supine positions showed no significant
main effects for drug treatment conditions. While all
cardiovascular variables showed normal circadian changes over
the course of the session, these changes were not related to
drug treatment. Most measures of blood pressure showed
decreases in the early portion of the session (1-4 hours)
with small increases as the session progressed, and this
trend was most pronounced in placebo-treated subjects on the
measure of standing systolic blood pressure.

No significant differences in the pattern of drug treatment
effects over the course of the session were observed on any
of the other blood pressure measures. While some subjects
showed increases in blood pressure at some point during the
session, these increases were not related to PPA
consumption. These phenomena were transient, quite variable
and can be considered anomalous (see also Section II.C. above
and References 22, 23, 24). These anomalous increases
occurred with the same frequency under both placebo and
active drug treatments. For a detailed presentation of
results showing the absence of clinically significant
differences between the drug treatment groups on the measures
of cardiovascular response see Table 1 on page 689 of
Reference 6.

In summary, Liebson et al. (6) conclude that:

> "PPA at a dose of 25 mg t.i.d. or 75 mg SR
> produced no significant change in pulse or
> blood pressure which was detectable using a
> parallel groups design. In the crossover
> study, however, small but statistically
> reliable differences between PPA 75 mg SR and
> placebo were identified. The finding of
> statistical significance can be attributed to
> the increased statistical power of the
> crossover design. In such designs, it is
> quite possible to identify statistically
> reliable effects that are clinically
> trivial. In the crossover study, for
> example, mean blood pressure differences
> between drug treatment conditions ranged from
> 0.83 mm Hg (standing systolic) to 3.37 mm Hg
> (supine diastolic) with an average overall
> difference of less than 2 mm Hg." (Reference
> 6 at page 691.)

Liebson et al. conclude:

> "Within the framework established in this
> trial, however, our results are quite
> consistent with the position that products
> containing PPA at currently marketed dosages
> do not pose a unique cardiovascular or

behavioral risk for normal, healthy adults
who read and follow the package and/or label
instructions." (Reference 6 at page 692.)

7. Mitchell, C.A.: Possible cardiovascular effects of
    phenylpropanolamine and belladonna alkaloids. Curr. Ther.
    Res. 10: 47-53, 1968 (Reference 7)

Mitchell (7) has reported two blinded, crossover assessments
on the effects of PPA and the combination of PPA and
belladonna alkaloids on seated blood pressure and pulse rate
in healthy, normotensive volunteers.

In the first study, blood pressure and pulse rate were
measured once daily in 32 subjects (20 males, 12 females)
with a mean age of 24.5 years (range 19-53 years) during one
week of no-treatment and 5 days of b.i.d. treatment with
placebo, a 50 mg sustained release formulation of PPA and 50
mg PPA plus 0.25 mg belladonna alkaloids in a sustained-re-
lease formulation.

A second, smaller study involving 6 subjects with a mean age
of 23 years (range 21-27) was conducted to assess the
possibility that short-lived blood pressure and pulse rate
effects occur soon after ingestion of a PPA-belladonna
alkaloids combination administered in a sustained-release
formulation. In this study subjects were given single doses
of 2 capsules containing a total of 100 mg PPA SR and 0.50 mg
of belladonna alkaloids or placebo in random order and blood
pressure and pulse rate were measured every 15 minutes for 90
minutes and every 30 minutes for a further 90 minutes.

Blood pressure results for both studies are expressed in
terms of mean arterial pressure (MAP=DBP + 1/3 x (SBP -

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DBP)]. Blood pressure and pulse rate results of the first study revealed no evidence of drug effect on blood pressure, but do show significant pulse slowing only with the combination. BP and pulse rate results of the second study provided no evidence of drug effect. (See Table I and III. of Reference 7 for further details.)

No subject withdrew from either study for an adverse event. In the first study the frequencies of unwanted effects were similar for PPA and placebo, but dry mouth, sore throat and lethargy were significant (p<.05 by Yates corrected Chi square) more commonly encountered with the combination than the placebo. No adverse events are mentioned for the second study. (See Table II of Reference 7 for further details.)

In sum, Mitchell (7) concluded there were no significant changes in mean arterial blood pressure attributed to treatment with phenylpropanolamine, with or without belladonna alkaloids.

8.   Goodman, R.P. et al.: The effect of phenylpropanolamine on ambulatory blood pressure. Clin. Pharm. Ther. 40: 144-147, 1986 (Reference 8)

This report (8) describes a double-blind, placebo-controlled, randomized, crossover study of the single-dose and steady state effects (7 days) of PPA on blood pressure with 24 hour monitoring during rest as well as during unrestricted daily activity on days 1 and 6.

Eighteen normotensive, nonsmoking males, ages 22 to 34 years (mean 25 years) found to be healthy on physical examination were enrolled in the study. All were within 20% of ideal weight (mean weight 165 lbs — range 123-211 lbs).

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Subjects were randomly assigned to receive a commercial 75 mg sustained-release PPA capsule or placebo each am for seven continuous days. After a fourteen-day washout period, the alternate study medication was given for a second seven day period. Subjects were seen four times during "every study week" for blood pressure monitoring. Twenty-four hour continuous ambulatory blood pressure monitoring using a Holter blood pressure monitoring system was done on Days 1 and 6 of each study week. Monitoring began between 8 and 9 am on each study day and blood pressures were measured every 15 minutes during waking hours (6 am to 12 midnight) and every 30 minutes from midnight to 6 am. Weight and "casual, seated blood pressures" were measured at each visit.

All subjects completed the study. Subjects reported no side effects attributable to drug therapy and tolerated the ambulatory blood pressure monitoring device with "minimal complaints."

Drug treatment had no detectable effect on global 24 hour systolic blood pressure, diastolic blood pressure and heart rate during Day 1 or Day 6, or when two hour periods on Day 1 and Day 6 were compared individually. Except for a trend toward increased heart rate which did not reach statistical significance except at night during Day 6 on PPA, the study results reveal no evidence whatever of clinically significant effects of PPA on blood pressure, heart rate, or diurnal variations in blood pressure or heart rate.

Goodman et al. (8) state that the results of this study support the findings of previous studies of the safety of PPA used in recommended doses for approved indications.

Another clinical study in which a 24-hour blood pressure
Holter monitoring device was employed is Omori et al. (see
Section II.E., page 27 and Reference 16).

9. <u>Lake, C.R. et al.: The effects of phenylpropanolamine on
    human sympathetic nervous system function. Neuro. Psych.
    Pharmacol. 1:163-168, 1988 (Reference 9)</u>

    <u>Lake et al.</u> (9) found no adverse cardiovascular effects
    either after the first dose or after two weeks of daily
    administration of PPA.

    In a placebo-controlled clinical trial, Lake et al. (9)
    studied 14 healthy normotensive volunteers who took 75 mg
    phenylpropanolamine daily for 2 weeks. Vital signs, plasma
    catecholamine concentrations, and the effects of exercise
    were measured 1 and 2 hours after the first dose and again at
    the end of the 2-week dosing period. Heart rate and blood
    pressures were measured with the subject in the supine and
    standing positions, and after gripping a hand dynamometer for
    5 minutes. Blood samples were collected for measurement of
    plasma catecholamine concentrations.

    Although systolic blood pressures for both the supine and
    standing positions and for all sampling times were
    significantly higher when the subjects were taking PPA than
    when they were taking placebo ($F = 5.95$, $p = 0.03$), the
    increases in blood pressure (3 mm Hg) were not clinically
    significant and no substantial changes in catecholamine
    concentrations were found. No statistical differences in
    diastolic blood pressure was found between placebo and PPA.
    Strenuous isometric exercise did not cause any greater
    increase in blood pressure or catecholamine concentrations
    after the subject took PPA than when they took placebo.

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While Lake et al. (9) question whether or not the small (< 3 mm Hg), yet not clinically meaningful, increases in systolic blood pressure seen in their healthy subjects might pose a problem for hypertensive obese patients, this theoretical suggestion has little foundation in light of studies by Unger (13), Bradley (14) and Omori (15; see Section II.E. below).

Lake et al. (9) conclude "recommended doses of PPA have only minimal sympathetic nervous system and cardiovascular effects in young, healthy, normotensive populations" under the conditions tested.

10.   Saltzman, M.B. et al.: Comparison of effects of two dosage regimens of PPA on blood pressure and plasma levels in normal subjects under steady state conditions. Drug Intell. Clin. Pharm. 17: 746-750, 1983 (Reference 10)

Saltzman et al. (10) reported no evidence of elevated blood pressure was noted in volunteers given daily doses of 75 mg PPA (25 mg immediate-release formulation TID or 75 mg sustained-release formulation) for 4 days. Also, there was no correlation between plasma concentration of PPA and blood pressure. The investigators concluded that the data demonstrate the safety of PPA daily doses of 75 mg in divided doses as well as in reliable sustained-release formulations in non-obese, normotensive subjects.

Saltzman et al. (10) used a randomized, open, crossover design in which 14 normotensive non-obese, nonsmoking males, age 20-40 (average 27 years) were given 25 mg PPA at 0, 4 and 8 hours for 4 days or 75 mg PPA SR (sustained-release) per day for 4 days. During the treatment phase subjects were

confined to a "live-in facility." After a 10-day washout the
alternate regimen was administered. Drugs, caffeine and
alcohol were proscribed during the study period. Blood
pressure and pulse (supine and standing) were recorded at
baseline and 1/2, 1 and 2 hours post-dosing on days 1, 2, and
3 and hourly on day 4 for 12 hours post- dosing. Prior to
entering the study each subject underwent a complete physical
examination and laboratory screen to insure freedom from
cardiovascular, gastrointestinal, liver or kidney disease.
The physical examination and laboratory screen were repeated
at the end of the study. PPA plasma levels were assayed on
day 4 to obtain steady-state values.

Mean values for systolic and diastolic blood pressure and PPA
blood levels on day 4 were the same for both regimens.
Diastolic blood pressure >90 mm Hg was found in only one
subject (96 mm Hg) on the 25 mg t.i.d. regimen -- 7 hours
after the start of the study and 3 hours after his second 25
mg dose of PPA. In this subject the peak plasma level of PPA
was not reached until 2 hours after the 3rd dose.

Three times daily, immediate release 25 mg PPA dosing
produced three well-defined peak blood levels of the drug,
while controlled release 75 mg PPA produced a single peak PPA
level at 4-6 hours after dosing.

The results of this study indicate that, with 95% confidence,
the "true" mean amount of PPA absorbed with the
sustained-release formulation is within 10.4% of the "true"
mean amount absorbed after dosing with the t.i.d. immediate
release regimen. There were no "clinically significant"
changes in the laboratory tests and there were no spontaneous
reports of discomfort during the study.

Saltzman et al. (10) compare their results with those of Renvall and Lindqvist (4), Mitchell (7) and Unger (13) — all of which reported no significant elevation in blood pressure with PPA doses up to 100 mg per day.

11. Silverman, H.I., et al.: Lack of side effects from orally administered phenylpropanolamine and phenylpropanolamine with caffeine: a controlled three-phase study. Curr. Ther. Res. 28(2): 185, 1980 (Reference 11)

A three-phase multisite study was designed to determine the cardiovascular effects of orally administered 25 mg immediate release (IR) PPA alone and in combination with 100 mg of caffeine (11). Silverman et al. (11) observed no statistical differences at the 95% confidence level — and therefore no clinically meaningful differences — in either systolic or diastolic blood pressures with respect to either test preparation based on baseline values throughout the study.

Thirty-seven healthy normal males, divided into three separate groups, received either PPA alone in a single blind design (n = 15), PPA plus caffeine in an open acute study (n = 10), or PPA alone and a placebo in crossover design (n = 12). Supine blood pressures and pulse rates were measured immediately prior to drug administration and at 30- or 60-minute intervals over a 4-hour period after administration.

As mentioned, none of the three treatment groups showed statistically significant changes in systolic and diastolic blood pressures at any measurement intervals. While Group I (25 mg immediate release PPA) showed a significant drop in pulse rate relative to baseline value at the 120 minute

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measurement interval only, neither of the other groups (i.e., 25 mg IR PPA plus 100 mg caffeine or 25 mg IR PPS vs. placebo in crossover design) showed significant changes in pulse rates.

Silverman et al. (11) conclude:

> "The present three-way study determined that 25 mg of phenylpropanolamine hydrochloride or 25 mg of phenylpropanolamine hydrochloride together with 100 mg of caffeine cause no mean increases in systolic or diastolic blood pressure in adults. In the clinically useful dose range, phenylpropanolamine is considered to be essentially an alpha agonist which undoubtedly accounts for our not finding a potentiation of caffeine's chronotropic action. The unexpected drops in pulse rate noted in group one subjects may have occurred as a result of a decrease in anxiety following the initial examination.

> "The fact that we found no significant differences in blood pressures in all three study groups leads us to conclude that doses of 25 mg of phenylpropanolamine hydrochloride alone or when combined with 100 mg of caffeine are not likely to adversely effect the myocardium nor cause a vasopressor response. Evaluation of adverse reports in the literature show them to be individual uncontrolled case reports where patients consumed other agents concurrently or were provided with doses far in excess of what is considered to be safe and effective."   (Reference 11)

12.   Aselton, P., and H. Jick: Phenylpropanolamine exposure and subsequent hospitalization. JAMA 253 (7): 977, 1985 (Reference 12)

Aselton and Jick (12) reported on their review of the Group Health Cooperative of Puget Sound database relative to the use of cough and cold preparations containing PPA and the

subsequent need for hospitalization for malignant hypertension, arrhythmia, psychiatric illness, and nonhemorrhagic stroke. They concluded:

> "These data indicate that the risk of hospitalization for the disorders studied attributable to taking PPA-containing cough and cold remedies used at Group Health Cooperative, _if present at all_, is very small." (Reference 12 at page 977; emphasis supplied.)

This conclusion is based on an analysis of 253,334 prescriptions filled for PPA-containing products at cooperating pharmacies for members younger than 65 years of age. For purposes of the analysis, Aselton and Jick assumed that each person filling a prescription for a PPA-containing preparation was at risk for one of the disorders studied for 30 days after the prescription was filled. This results in 7,600,020 persons-days at risk for hospitalization among PPA users. Taking the whole population of the Group Cooperative younger than 65 years as person years, multiplying by 365, and subtracting the days at risk for PPA users during the period 1977 through 1982 yields 521,618,672 person days at risk among nonusers of PPA.

The summary of the results of Aselton and Jick's analysis is given in the following table:

Observed Risk for PPA Users

	Subjects Taking PPA		Subjects Not Taking	
	Number of Subjects	Incidence in Group	Number of Subjects	Incidence in Group
Cerebral Hemorrhage	1	1.54×10^{-7}	113	2.65×10^{-7}
Malignant Hypertension	0	0	20	3.83×10^{-8}
Arrhythmia	0	0	313	6×10^{-7}
Acute Psychiatric Disorders	2	2.63×10^{-7}	106	2.03×10^{-7}
Thrombotic or Nonspecific CVA	1	1.31×10^{-7}	275	5.27×10^{-7}

The conclusion that the risk of such events from PPA use —
"if they occur at all, is small" was not affected by changing
the assumption about the risk period from 30 days to 90 days.

E.   Studies of PPA in Special Populations

Several studies (13, 14, 15, 16, 17, 18) have been published which
have assessed the effects of PPA — alone or in combination — in
special populations of patients (n = 151), including controlled
hypertensives with asthma, obesity, and/or hyperglycemia and and
the rare group of patients with severe autonomic impairment. Table
C (pages 23a, b) is a summary of key findings from these studies on
PPA use in special patient populations. A review of Table C shows
that each of these studies supports the safety of PPA. Taken
together with the data on normotensives (Section II.C. above),
these studies support the continued OTC availability of PPA. Brief
descriptions of the studies of PPA in special populations are given
below.

1.   Unger, D.L. et al.: Effects of an antiasthmatic compound on
      blood pressure of hypertensive asthmatic patients. Ann.
      Allergy 25:260-1, 1967. (Reference 13)

      Unger et al. (13) designed their study to evaluate the effect
      of an antiasthmatic compound, Asbron, containing PPA 25 mg,
      glyceryl guaiacolate 100 mg and theophylline sodium glycinate
      300 mg on blood pressure in hypertensive asthmatic patients.
      Eleven female and 10 male patients, all hypertensive (i.e.,
      all had either systolic blood pressure > 140 or diastolic
      blood pressure > 90 or both) presumably on no medication (no
      further descriptors provided) had their blood pressures
      checked 3 times within 5 minutes prior to treatment and the
      results averaged for each patient. The patients were then

TABLE C

SUMMARY TABLE OF KEY FINDINGS FROM PIVOTAL STUDIES ON
SPECIAL POPULATIONS OF PATIENTS

DOSE REGIMEN	TOTAL STUDY N	BASELINE	KEY FINDINGS
Unger et al. (Reference 13)			

Multiple dose
25 mg IR PPA plus
   100 mg glyceryl
   guiacolate and
   300 mg theophylline
t.i.d. until next visit
	21	hypertensive asthmatic	Investigators conclude PPA in combination with glyceryl guaiacolate and theophylline does not raise blood pressure in dose used

Bradley and Raines (Reference 14)			

Multiple dose
25 mg IR PPA + 100
   mg caffeine t.i.d.
75 mg SR PPA o.d.
placebo
 	
6 weeks (2 weeks on each
   therapy) crossover
	12	hypertensive obese	No statistically significant differences between baseline and end of treatment values for blood pressure or heart rate

Bradley and Raines (Reference 15)			

Multiple dose
25 mg IR PPA plus
   100 mg caffeine
   t.i.d
placebo
t.i.d./6 weeks
	72	hypertensive obese	No clinically meaningful changes in blood pressure or heart rate in group on PPA and no significant differences in these parameters between PPA and placebo

Omori (Reference 16)			

Multiple dose
25 mg IR PPA q.i.d.
   hours for 2.5
   days
crossed over to placebo
	26	hypertensive	No clinically significant changes in blood pressure

Krosnick et al. (Reference 17)			
Multiple dose 75 mg SR PPA b.i.d./2 weeks	6	hyperglycemic obese	No differences between treatments re: heart rate, blood pressure or fasting glucose concentrations

TABLE C (continued)

DOSE REGIMEN	TOTAL STUDY N	BASELINE	KEY FINDINGS
Biaggioni et al. (Reference 18)			
Single dose 25 mg and 12.5 mg IR PPA	14	autonomic dysfunction	Pressor effect due to PPA seen in patients with rare disorder of severe autonomic dysfunction (which itself is seen as orthostatic hypotension and a subnormal norepinephrine response to upright posture) PPA considered potentially therapeutic in these patients

asked to take 1 Asbron tablet t.i.d. (with meals) until their next visit. Upon return, 3 blood pressure readings were again taken and averaged. Patients were also questioned about any side effects that may have occurred (presumably those thought to be caused by the medication).

Baseline blood pressure readings averaged 166/102 mm Hg and the on-treatment average was 166/101 while median blood pressures were 164/104 mm Hg before and 168/102 mm Hg after medication. Five patients had an elevation and another five experienced a drop in systolic blood pressure of 10 mm Hg or more on therapy. Similarly, there were 4 patients each with an elevation or drop in diastolic blood pressure of 10 points or more. Three patients complained of "slight nervousness," but none discontinued the medication.

Unger et al. (13) conclude that Asbron does not raise blood pressure in the dosage used in the study. It is of some interest that the administration of PPA with theophylline, which might on theoretical grounds have been expected to result in potentiation of PPA's vasoactive actions, apparently resulted in no measurable effects on blood pressure.

2. Bradley, M.H. and Raines, J.: Single-blind safety and efficacy evaluation of phenylpropanolamine HCl in obese patients with controlled hypertensive disease. Presented at: Fifth Annual Meeting of the North American Association for the Study of Obesity, Banff, Alberta, Canada, August 25-28, 1988 (Reference 14)

The effectiveness and safety of phenylpropanolamine HCl as an appetite suppressant for use by adult obese patients with stable, controlled hypertensive disease was evaluated (14).

The study population for the initial 6-week, single-blind, crossover study was three males and nine females, 25-27 years old, with exogenous obesity (12-54% overweight), and stable, controlled hypertensive disease. For weeks 1 and 2, patients were given 25 mg PPA plus 100 mg caffeine t.i.d. one hour before meals; a washout period followed for weeks 3 and 4 during which patients took placebo b.i.d.; for weeks 5 and 6 patients took a single daily dose of 75 mg PPA.

Two patients discontinued the study after the first 2-week phase due to protocol violations; neither reported any adverse reactions. Of the ten patients who completed the study, only one reported side effects; these were feelings of dizziness and nausea during the first week of medication (25 mg PPA plus 100 mg caffeine t.i.d.), but it could not be determined whether these were related to the medications or diet. No statistically significant differences between baseline and end-of-treatment values were noted for blood-pressure or heart-rate determinations. No significant blood-pressure or heart-rate differences were noted within each of the three 2-week test periods, or among the three periods. Patients lost an average of 1.9 pounds/week when taking 25 mg phenylpropanolamine plus 100 mg caffeine t.i.d., and 1.4 pounds/week when taking a single 75 mg dose of phenylpropanolamine; during the washout (placebo) phase, patients lost an average of 0.63 pounds/week.

Bradley (14) concluded that phenylpropanolamine at either dose was safe and effective in a population of obese patients with stable, controlled hypertensive disease.

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3.   <u>Bradley, M., and J. Raines: Double-blind safety and efficacy
evaluation of phenylpropanolamine HCl in obese patients with
controlled hypertensive disease.   Presented at: Fifth Annual
Meeting of the North American Association for the Study of
Obesity, Banff, Alberta, Canada, August 25-28, 1988</u>
(Reference 15)

In a second study, <u>Bradley and Raines</u> (15) observed no
significant differences in standing or supine blood pressures
or heart rate between groups of hypertensive patients given
either 25 mg PPA HCl t.i.d. plus dietary restrictions or
placebo plus diet for 6 weeks; PPA was significantly superior
to placebo in suppressing appetite and produced significantly
greater weight loss. Neither treatment resulted in any
adverse reactions.

Seventy-two adult obese outpatients with stable, controlled
hypertensive disease entered this randomized, double-blind,
parallel-groups study conducted over 6 weeks. The PPA and
placebo groups were comparable in background characteristics
including age, marital status, body frame, baseline body
weight, ideal body weight, and percent overweight. All
participants were required to follow a daily 1250-calorie,
nutritionally balanced diet plan throughout the study.

Compared to baseline values, there were no clinically
significant changes in blood pressures or heart rate in the
group given PPA. In addition, there were no significant
differences in these values between the two treatment groups.
PPA was significantly superior to placebo in suppressing
appetite. There was a significant difference in mean
cumulative weight loss per week between the PPA (0.79
pound/week) and placebo (0.50 pounds/week) groups.

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Sixty of the 72 patients completed the 6-week study; eight given PPA and four given placebo withdrew for various reasons unrelated to treatment. It could not be determined whether the subjective side effects reported (insomnia, tingling hands, weakness, itchy scalp, allergic pruritis, urinary frequency, unstable angina, dizziness) were related to the study medication or diet. The investigators concluded that PPA is safe and effective, for obese patients with controlled hypertensive disease.

4.   Omori, D.M. et al.: Does phenylpropanolamine affect blood pressure in mildly hypertensive patients? Presented at the Meeting of the Society of General Internal Medicine: American College of Physicians, Washington, D.C. (1988) (Reference 16)

Omori et al. (16) found that, when taken at recommended doses (25 mg q.i.d.), PPA did not cause clinically significant changes in blood pressure or heart rate in patients with stable, mild hypertension.

In this prospective, double-blind, placebo-controlled, crossover study entering subjects had stable, mild hypertension (systolic blood pressure < 160 mm Hg; diastolic blood pressure < 100 mm Hg) and were on: (1) no drugs; (2) a diuretic; (3) an angiotensin-converting-enzyme inhibitor; (4) a beta-blocker; or (5) a combination of these drugs. Subjects were randomly assigned to take PPA or placebo for 2 and 1/2 days during the first week of the study; the following week the treatment groups were reversed. On the second day of each treatment, ambulatory blood pressures were measured using a 24-hour blood pressure recorder (Holter). The dose of PPA was 25 mg every 4 hours

(100 mg total daily dose). To adequately evaluate the cardiovascular effects, ambulatory blood pressures and heart rates were monitored continuously for 24 hours during treatment with PPA.

Twenty-six subjects whose mean age was 57 years participated in the study. The mean differences in the cardiovascular values for the 24-hour recordings in the phenylpropanolamine- and placebo-treatment groups were: systolic blood pressure, 0.4 mm Hg ($p > 0.5$); diastolic blood pressure, 1.2 mm Hg ($p > 0.2$); and heart rate, 0.4 beats per minute ($p > 0.5$). No adverse reactions were noted. It was concluded that "PPA does not cause clinically significant increases in blood pressure and can be safely used in the stable, mildly hypertensive patient." (Reference 16)

Another clinical study in which a 24-hour blood pressure Holter monitoring device was employed is Goodman et al. (see Section II.C. and Reference 8).

5.   Krosnick, A. et al.: Negative results with phenylpropanola- mine in hyperglycemic patients. Presented at the Third Annual Regional Meeting of the Philadelphia, Delaware, and New Jersey Chapters of the Society for Neuroscience, Philadelphia, PA, (1982) (Reference 17)

When given at the relatively high dose of 150 mg per day, Krosnick et al. (17) observed that PPA produced no significant changes in blood pressure or heart rate in obese, hyperglycemic patients.

In a double-blind, placebo-controlled, crossover clinical trial, six obese, hyperglycemic patients took 75 mg

sustained-release phenylpropanolamine or placebo twice daily
for 2 weeks. Body weight, heart rate, blood pressure, and
fasting blood glucose concentrations were recorded three
times weekly.

Analysis of variance showed there were no significant dif-
ferences between phenylpropanolamine- and placebo-treatment
groups re: heart rate, blood pressure or fasting glucose
concentrations. One patient complained of adverse reactions
(dizziness) and was told to take one capsule daily instead of
two.

6.   Biaggioni, I. et al.: The potent pressor effect of phenylpro-
      panolamine in patients with autonomic impairment. JAMA
      258(2): 236-9, 1987 (Reference 18)

      Biaggioni et al. (18) studied patients with severe autonomic
      impairment and found 25 mg PPA can produce significant
      increases in systolic, diastolic and mean arterial blood pres-
      sures within 30 minutes post dose. Biaggioni et al. state
      they have used this PPA-induced pressor effect thera-
      peutically "to improve the functional capacity of patients
      with orthostatic hypotension." Placebo control arms were not
      used in this study.

      Biaggioni et al. (18)[1] conducted an open, single oral dose

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[1] It is of some interest that the investigators make the following some-
     what revealing assertion in their introduction: "The dextroisomer of
     phenylpropanolamine is much more potent than the racemic mixture of
     the drug, which is the only form available in many countries." PPA in
     the U.S. is racemic norephedrine. Most studies in which the relative
     potencies of the 1- and d-isomers of norephedrine have been compared
     have found 1-norephedrine significantly more vasoactive than d-norephe-
     drine. On the other hand, d-norpseudoephedrine, yet another stere-
     oisomer of PPA, has been found to be a more potent vasoactive
     substance than 1-norephedrine in some studies. The investigators'
     statement reflects the confusion frequently engendered by the rela-
     tively complex stereochemistry of PPA. (See Section IV. below for
     further details.)

study of the pressor effects of PPA in 14 patients with
autonomic dysfunction -- the seven males and seven females
studied ranged in age from 55 to 80 years (mean 66.78). All
patients had efferent autonomic failure characterized by
orthostatic hypotension, abnormal autonomic reflexes and an
abnormal norepinephrine response to upright posture (i.e.
subnormal increase).

Patients were admitted to the study center at least three
days prior to dosing. All medications and methylxanthine-con-
taining beverages were proscribed. A diet containing 3.45 gm
sodium and 3.12 gm potassium daily was provided. Studies
were performed with patients fasting in the seated position.

One of the patients was an insulin-dependent diabetic and his
dysautonomia was thought caused by diabetes. Three patients
were thought to have Shy-Drager Syndrome (autonomic failure
associated with central nervous system abnormalities and
degeneration of preganglionic sympathetic neurons and
characterized by normal basal blood levels of norepinephrine,
lack of supersensitivity to the blood pressure elevating
effects of norepinephrine -- e.g., tyramine). Ten of the
patients had idiopathic autonomic failure (also referred to
as primary orthostatic hypotension). Idiopathic autonomic
failure is associated with degeneration of post-ganglionic
sympathetic neurons, is not associated with central nervous
system abnormalities, and is characterized by low basal blood
norepinephrine levels, supersensitivity to the pressor
effects of i.v. norepinephrine and blunted responses to drugs
which cause release of norepinephrine.

Blood pressure and heart rate were recorded automatically
every five minutes with an oscillometric blood pressure

monitor (Dinamap) "to reduce observer bias" and results expressed as the mean of the three values for each 15 minute observation period.

After a 13 minute baseline period, nine patients were given 25 mg immediate release PPA tablets. Because of significant pressor effects in the supine position seen in this group of nine patients, 12.5 mg PPA was given to five subsequent patients who had severe orthostatic hypotension. Blood pressure and heart rate were measured for 105 minutes after dosing. Mean arterial blood pressure was calculated as 1/3 systolic plus 2/3 diastolic pressure.

Regarding the first group of nine patients, all but two of the patients were significantly hypertensive in the supine position (a characteristic of dysautonomic patients), all had profound decreases in blood pressure and most had minimal change in heart rate on standing. Mean systolic blood pressure, diastolic blood pressure and mean arterial pressure all increased significantly and plateaued about one hour post-dosing in the nine patients given 25 mg PPA. There was no change in mean heart rate after administration of 25 mg PPA. Systolic blood pressure and diastolic blood pressure responses to 25 mg PPA among the five patients designated "severe" (i.e., orthostatic decrease in systolic blood pressure of > 90 mm Hg) were significantly greater than in the four patients not considered severely affected by 25 mg PPA. Despite maximal systolic blood pressure increases of 71 and 77 mm Hg and maximal diastolic blood pressure increases of 36 and 38 mm Hg no patient reported symptoms.

Since very large blood pressure responses were seen in the first nine patients (who had been treated with 25 mg PPA),

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the next five patients, who as a group were "more severely
affected," were given only 12.5 mg PPA. The mean maximal
orthostatic decrement in systolic blood pressure for these
five patients was 106 ± 6 mm Hg. The lower dose of PPA (12.5
mg) caused changes in systolic blood pressure, diastolic
blood pressure and mean arterial pressure similar to those
seen with the 25 mg dose and, as with the higher dose, no
change in mean heart rate was seen.

In their discussion, Biaggioni et al. (18) indicate that they
have seen significant hypersensitivity to the pressor effects
of alpha$_1$-agonists and to the hypotensive effects of
beta-agonists in dysautonomic patients. They also point out
that PPA is thought to cause its vasoactive effects by both
direct and indirect mechanisms and hence, the study results
were not at all unexpected. Interestingly, the investigators
consider the PPA effects they demonstrated to be potentially
therapeutic and state they have treated some of their
dysautonomic patients with the drug.

Of importance is the fact that autonomic impairment of the
magnitude described in this study is very rare, and because
of their symptomatology such patients would be aware of their
condition and under a doctor's care. And, as mentioned
above, a doctor might well consider PPA of therapeutic value
in certain of these patients.

F.   Additional Commentary on Published Clinical Studies

This section discusses three studies by Pentel et al. (53, 54) and
Lake et al. (55) who have reported effects of PPA on blood pressure
that are not entirely consistent with the main weight of the
published literature and the recent studies described in Sections

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II.D., II.E. and III. in this Statement. The Pentel and Lake studies — using study populations sizes of 10, 6 and 6 respectively — provide support for the important conclusion that PPA does not produce clinically meaningful changes in standing or sitting blood pressure at OTC recommended doses (25 mg IR or 75 mg SR). These studies report meaningful increases in supine blood pressure in normotensive nonobese subjects given a 75 mg immediate release dose of PPA (Pentel et al. 54) or given two 75 mg sustained-release capsules of PPA (Lake et al., 55).

In apparent contradistinction to these studies are the findings of Renvall and Lindqvist (4) who reported on a study population of 70 that they observed no elevation in blood pressure in normotensive, nonobese subjects on 50 mg b.i.d. or 100 mg b.i.d. immediate release PPA for three days.

Given the differences in findings among these studies, three very recent studies have been sponsored by SmithKline Consumer Products (19, 20) and CIBA Consumer Pharmaceuticals (21), as described in Section III below. These additional studies support the work of Renvall and Lindqvist (4) that the dose associated with significant cardiovascular effects is at least three times the dose of PPA recommended for OTC usage in Canada and the United States.

Of additional importance are the findings by Blackburn et al. (2) on a study population of 881 subjects that the magnitude of the pressure effect depends on baseline intrinsic sympathomimetic activity — a finding supported by the data presented above on effects of PPA in hypertensive individuals (See Table C; pages 23a, b). As pointed out by Blackburn et al. (2), "those subjects whose safety was most feared for, the obese, those with slightly elevated blood pressure, or any augmented intrinsic sympathomimetic activity have an equal or even greater safety margin." This finding is also

supported by Pentel's claim (53) of an inverse relationship between the mg/kg dose of PPA and the greatest observed increase in blood pressure (although, see immediately below). Additionally, the SmithKline Consumer Products study demonstrates a tachyphylactic response to multiple doses of PPA which would further widen PPA's margin of safety as an OTC ingredient.

Explanations for the differences among these studies may be based on a number of considerations:

a. Pentel (53, 54) and Lake (55) used small numbers of subjects and made no effort to screen out placebo responders as was the case, for example, for the SmithKline Consumer Products and CIBA Consumer Pharmaceuticals studies (19, 20, 21).

b. The study by Pentel et al. (53) reported that the relationship between the mg/kg dose of PPA and the greatest increase in supine systolic (but not diastolic) blood pressure was based on one individual, the exclusion of which reduced the results to nonsignificance. Such sensitivity in the database makes the findings suspect.

c. As stated by Morgan et al. (56) in relation to the first part of the second Pentel study (54),

> "More important is the realization that the experiment was uncontrolled. The authors report that the procedure was double-blind, but this refers to the dosing of propranolol; PPA dosing was uncontrolled. All five subjects were given two doses of [immediate-release] PPA on successive days in the same order, 37.5 mg followed by 75 mg. The outcome of this treatment was an uncontrolled mixture of drug effect and anxiety caused both by drug dosing and the experimental procedure. This is not a minor criticism." (Emphasis supplied)

Morgan et al. (56) also find inherent bias in the study design of the second part of the second Pentel study and states:

> "This experiment was even more potentially influenced by <u>an order effect</u> than was the first experiment. In all six subjects, propranolol was given on the first day and placebo on the second. Hence any learning effect or diminution of anxiety caused by drug dosing, indwelling catheters, and the like was given maximum play. The battery of hemodynamic effects is thus compromised and yield little of value, because propranolol was operating against a mixture of drug effect, anxiety and other factors."
> (Emphasis supplied)

Morgan et al. (56) conclude the Pentel study (54) is "an inadequately controlled experiment."

d.   The safety profile of PPA is augmented through analyses of adverse drug reactions (ADRs) reputed to be associated with PPA in the published literature and in FDA's Spontaneous Reporting System (See Section V). These ADR analyses do not support the concerns raised by Pentel et al. (53, 54) and Lake et al. (55) and demonstrate from market experience an acceptable margin of safety for PPA which can also be drawn from the available clinical data presented above.

Complete reports of the Pentel et al. (53, 54) and Lake et al. (55) studies can be found in the Appendix.

III. RECENT PIVOTAL STUDIES SUPPORT THE SAFETY
OF PPA AS AN OTC INGREDIENT

Three recent studies (19, 20, 21) performed by SmithKline Consumer Products and CIBA Consumer Pharmaceuticals add additional support for the safety of PPA as an OTC active ingredient. These studies were done using protocols negotiated between the sponsors and the U.S. Food and Drug Administration (FDA) and are consistent with the published data discussed above in Sections II.D. and II.E. in normotensive subjects and special patient populations. A summary of the key findings from these studies is provided in Table D (page 36a).

From these recent studies, the following conclusions can be made:

1. a. A reduction in the pressor response after multiple doses of PPA — a tachyphylactic effect — occurs with successive doses of 100 mg PPA when administered as an acute dose after several placebo days, after b.i.d. 50 mg PPA dosing, and when given as a single daily dose for 5 days (Reference 19);

    b. This tachyphylactic effect is a favorable attribute of PPA when considering multiple dose therapy for cough/cold symptoms, for example;

2. The dose of PPA associated with significant cardiovascular effects is at least three times the dose of PPA recommended for OTC usage in Canada and the United States (Reference 20);

3. Increases of 10 and 20 mm Hg in diastolic and systolic blood pressures, respectively — which are well within the the normal range of 24 hour blood pressure variations described by Pickering et al. (2) and Harshfield et al. (Reference 3; see also Section II. B. above) — would be expected to occur with immediate release PPA in solution form at a dose of 120 mg — approximately three times the OTC cough/cold dose (Reference 21).

TABLE D

SUMMARY TABLE OF KEY FINDINGS FROM RECENT NONPUBLISHED STUDIES

Dose Regimen	Total Study n	Baseline	Key Findings
SmithKline Consumer Products (Reference 19)			
Multiple dose 100 mg IR qd on days 5-15** 50 mg IR PPA on days 5-9 & 11-14** and 100 mg PPA on days 10 and 15** 100 mg IR PPA on days 10 and 15** ** Placebo: given on the other days of the 17 day study	15	healthy volunteers	Data demonstrate a tachyphylactic pressor response with success-ive doses of 100 mg PPA when administered as an acute dose after several days on placebo after b.i.d. dosing, and when given as a single daily dose
Ryan et al. (Reference 20)			
Ascending doses 50, 75, 150, 250 mg IR PPA placebo	15	healthy volunteers	The dose of PPA associated with significant cardiovascular effects is at least three times the recommended OTC dose
CIBA Consumer Pharmaceuticals (Schumann et al., Reference 21)			
Ascending doses 12.5, 25, 50, 75, 100, 125, 150 mg IR PPA	12	healthy volunteers	"Meaningful increases" in blood pressure were seen first at 100-125 mg IR PPA. Computer modeling projected "meaningful increases" at 120 mg IR PPA.

IR = immediate release
SR = sustained, or controlled, release

A brief description of these studies (19, 20, 21) follows, and more
detailed reports of the same studies can be found in the Appendix.

A.   SmithKline Consumer Products: Cardiovascular safety of oral
      multiple doses of phenylpropanolamine (Reference 19)

      SmithKline Consumer Products undertook a study (19) to determine
      whether successive doses of PPA would be associated with a
      tachyphylactic pressor response. In fact, this was found to be the
      case.

      Fifteen adult male subjects identified as responders to the pressor
      effects of high doses of PPA completed this 17-day double-blind,
      placebo controlled, parallel tachyphylaxis study.

      Subjects were randomly assigned to one of the following three
      regimens:

      A.   PPA 100 mg qd (Days 5-15), placebo (Days 16-17)

      B.   PPA 50 mg bid (Days 5-9, 11-14), PPA 100 mg (Days 10 and 15),
            placebo (Days 16-17)

      C.   Placebo (Days 5-9, 11-14), PPA 100 mg (Days 10 and 15),
            placebo (Days 16-17)

      All subjects received no dosing on Day 1, placebo on Days 2 and 3
      and PPA 100 mg on Day 4. On Days 2 and 3, if blood pressure
      increases were more than 25/15 mm Hg or more than 30% over peak
      baseline day in the same position (supine or erect), the subject
      was identified as a placebo responder and discharged from the
      study. Nine of 39 entered subjects were identified as placebo
      responders and discontinued from further study.

On Day 4 only those subjects with peak blood pressures exceeding 170 mm Hg systolic or 100 mm Hg diastolic, or 50% of peak Day 3 value in the same position continued on the study and were randomized to the aforementioned regimens. Nine of the 30 remaining entered subjects were discontinued because their Day 4 blood pressure peak readings were too low.

If at any time peak after-PPA-dosing blood pressures exceeded 200 mg Hg (or 60% over baseline) systolic or 110 mm Hg diastolic in either position, the subject was discharged from the study. One subject was discontinued from further study when his systolic blood pressures exceeded 60% baseline after the initial Day 4 100 mg PPA dose. During active dosing, subject #6 was discontinued from further study after Day 10 (Regimen C - 100 mg PPA) when his supine systolic blood pressure exceeded 60% or peak at baseline. Of 39 entered subjects, 46% were discontinued from further study because of a placebo response during screen or too low blood pressure peaks after receiving 100 mg on Day 4.

Peak increases in supine blood pressure for Regimens A and B generally occurred 40 minutes to 1.5 hours after dosing, while peak supine blood pressures for Regimen C were quite variable. Peak increase over peak baseline for each regimen on Days 4, 10 and 15 (all subjects received PPA 100 mg qd) are given in Table E (page 39a).

Plasma PPA levels remained steady during Days 5-15, with Regimen A maintaining at approximately 13-15 ng/ml and Regimen B at 28-32 ng/ml. On Days 10 and 15 all regimens peaked between one and two hours, remained near peak levels for approximately four hours and then returned to steady-state levels by 20 hours for Regimens A and B and 48 hours for Regimen C.

The major subjective symptom reported was dizziness/light-headedness:

     Regimen A (100 mg dose)   — 5 complaints
     Regimen B (100 mg dose)   — 4 complaints
     Regimen C (placebo)   — 4 complaints
           (100 mg dose)   — 26 complaints

The number of subjects with no side effects were:

Regimen A — 2, Regimen B — 3, Regimen C — 0.

No significant changes were noted in cardiac rate or rhythm.

When normal males identified as responders to the pressor effects of PPA were given single daily doses of 100 mg PPA (Regimen A), 4 times the current approved single dose of 25 mg, the mean blood pressure peak decrease from the first to the last 100 mg dose was 29/13 in the supine position (169/99 to 140/86; 17% systolic decrease, 13% diastolic decrease) and 32/9 in the erect position (148/96 to 116/87; 21% systolic decrease, 9% diastolic decrease).

When subjects on Regimen B were given single daily doses of 100 mg PPA on the first, seventh and twelfth day between BID 50 mg PPA dosing, mean blood pressure peaks from the first to the twelfth day decreased by 28/14 in the supine position (175/98 to 143/84; 16% systolic decrease, 14% diastolic decrease) and decreased by 44/18 in the erect position (170/101 to 126/83; 18% diastolic decrease).

When subjects on Regimen C were given single daily doses of 100 mg PPA on the first, seventh and twelfth day between BID placebo dosing, mean blood pressure peaks from the first to the twelfth day decreased by 17/6 in the supine position (175/98 to 158/92; 10% systolic decrease, 6% diastolic decrease) and by 34/11 in the erect position (156/99 to 122/88; 22% systolic decrease, 11% diastolic decrease).

TABLE E

PEAK INCREASE IN BLOOD PRESSURE COMPARED TO PLACEBO ON CHALLENGE
DAYS 4, 10 AND 15

Regimen Day[1]	BP Mean		Peak Increase (Over Peak Baseline)	
	Supine	Erect	Supine	Erect
A Base	116/74	114/77		
4	169/99	148/96	53/25	34/19
10	144/90	127/85	28/16	13/8
15	140/86	116/87	24/12	2/10
B Base	116/78	124/79		
4	171/98	170/101	55/20	46/22
10	149/88	138/90	33/10	14/11
15	143/84	126/83	27/6	2/4
C Base	118/72	121/82		
4	175/98	156/99	57/26	35/17
10	167/94	150/95	49/22	29/13
15	158/92	122/88	40/20	1/6

[1]Regimens:

    A   PPA 100 mg qd (Days 5-15), placebo (Days 16-17)

    B   PPA 50 mg bid (Days 5-9, 11-14), PPA 100 mg (Days 10 and 15), placebo (Days 16-17)

    C   Placebo (Days 5-9, 11-14), PPA 100 mg (Days 10 and 15), placebo (Days 16-17)

The data demonstrate a tachyphylactic pressor response with successive doses of 100 mg PPA when administered as an acute dose after several days placebo (Regimen C), after BID 50 mg PPA dosing (Regimen B) and when given as a single daily dose (Regimen A). The reduction in the pressor response after multiple doses of PPA is a favorable attribute of PPA when considering multiple dose therapy for cough/cold symptoms, allergic symptoms and weight reduction.

B.   Ryan et al.: The relationship between single oral doses of PPA and pressor responses (Reference 20)

Ryan et al. (20) conducted a double-blind placebo-controlled parallel dose-range study in normal healthy volunteers to assess the cardiovascular changes with single oral doses of PPA. The study was specifically designed to push the dose of PPA high enou (up to 250 mg IR PPA) to observe and evaluate cardiovascular effects.

The results showed the dose of PPA associated with significant cardiovascular effects is at least three times the OTC recommended dose of 25 mg PPA.

Fifteen healthy adult males between 18 and 40 years of age, with body weights within 25% of their ideal weight, participated in this dose-range study.

One subject (#14) had an entry supine blood pressure of 132/80 (mean of 3 readings), while all others had entry supine blood pressures $\leq 130/85$ and supine heart rates ≤ 80 beats/minutes. No subject had a history of mental disorders or drug abuse, or family history of stroke, and no alcohol was consumed within one week prior to the study.

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Subjects were randomly assigned to one of the following two regimens (10 subjects - Regimen A; 5 subjects - Regimen B):

a.   Regimen A: Phenylpropanolamine HCl Capsules given at 0 hour on:

Day 4 - 1X 50 mg PPA cap., 4X placebo caps.
Day 7 - 1X 50 mg PPA cap., 1X 25 mg PPA cap., 3X placebo cap.
Day 10 - 3X 50 mg PPA caps., 2 placebo caps.
Day 13 - 5X 50 mg PPA caps.

On days 1-3, 5, 6, 8, 9, 11 and 12 subjects on Regimen A were given 5 placebo capsules.

b.   Regimen B: Placebo capsules given at 0 hour on Days 1 through 13.

After dosing the subjects stayed at rest in bed for 4 hours.

The objective study parameters criteria included the following:

a.   Vital signs (blood pressure and pulse rate) were measured in the supine position and after 1 minute standing specified times before and after drug administration.

b.   Within two weeks prior to the beginning of the study, a complete history, physical examination, CBC, SMAC-20, urinalysis with sediment, 12-lead EKG and chest X-ray (if not done within 6 months) was performed.

c.   Twenty-four hour Holter monitoring was performed eight different study days.

d.   10 ml blood samples for PPA plasma levels were collected at specified intervals pre and post dosing.

e.   In case of an indicator response, the investigator could
repeat the dose at his discretion on the next dosing day. If
on repeated dosing, the indicator response was not
reproduced, increased dosage could proceed according to
protocol. Indicator responses were defined as:

—   an increase of diastolic blood pressure $\geq$100 mm Hg or
to $\geq$50% over baseline

—   an increase of systolic blood pressure to $\geq$170 mm Hg or
to $\geq$50% over baseline

—   an increase in pulse rate to $\geq$140 bpm, or to $\geq$50% over
baseline

—   the appearance of abnormal PRS complexes or cardiac
conduction that did not occur during the placebo
period.

f.   Only the first data set for those subjects dosed twice at a
given level were used in data analysis.

g.   An EKG was done if an indicator response occurred or if there
was a subjective complaint.

Subjective responses were elicited at hourly intervals post dosing.

Regarding Results, a complete listing of responses for subjects
meeting the indicator criteria (see above) are listed in Tables F
and G (pages 42a and 42b). The data showed an increased occurrence
of indicator responses (BP $\geq$100 mg Hg diastolic or 170 systolic, or
increases $\geq$50% of baseline values) with of PPA. One of 10 subjects
responded at 50 mg, but the response was not reproduced on

TABLE F

INDICATOR RESPONSES

Regimen	Dose	(n)	Subject #	Response
A (Active)	50 mg	(10)	#12	Supine systolic BP 180 @ 40-60 min. Dose repeated - no indicator response continued
A (Active)	75 mg	(10)	#3 (black)	Supine systolic BP $\geq$ 50% baseline 40-60 min. (108/72 - 168/94). Repeated - BP 172 @ 40 min. @ 60 min.
			#15 (black)	Supine systolic BP 178 @ 40 min. Repeated BP 190, 188, 176 @ 40, 60, 80 min.
			#12 (black)	Supine systolic BP 194, 188 @ 40, 60 min. Repeated: $\geq$ 50% over baseline (108/56 - 160/86)
			#3, 15, 12	No further dosing
A (Active)	150 mg	(6)	#1	Supine systolic BP @ 80 min. 172 Orthostatic hypotension at 4 hr. (76/48)
			#11	Supine systolic BP 194, 184 @ 40, 60 min. Erect BP 184 @ 40 min. Repeated on rechallenge
			#14	Supine systolic BP 182-194 40-69 min. Erect systolic BP 178 @ 40 min. Supine diastolic BP 104-110 60-72 min. Given Catepres (PO)
			#1, 11, 14	No further dosing
A (Active)	250 mg	(2)	#9	Supine systolic BP 184, 178 @ 40-80 min. Supine diastolic BP 104-108 @ 40-100 min. Erect diastolic BP 104-108 @ 40"-2 hrs.
			#10	Supine systolic BP 186-270 40-120 min. Supine diastolic BP 102-110 80-120 min. Erect diastlic BP 106 @ 80 min. Given Catepres (PO)

TABLE G

OTHER RESPONSES

Regimen	Dose	Subject	Response
A (Active)	50 mg	#3	Day 4: Erect HR $\geq$ 50% base-line (78-122)
	75 mg	#14	Day 7: Supine diastolic BP $\geq$ 50% baseline
	Placebo	#4	Day 12: Erect diastolic BP $\geq$ 100
	Placebo	#9	Day 6: Erect HR $\geq$ 50% base-line
	Placebo	#11	Day 6: Supine HR $\geq$ 50% base-line
	Placebo	#15	Day 3: Supine HR $\geq$ 50% baseline Day 6: Erect HR $\geq$ 140
B (Placebo)	Placebo	#2	Day 7: Erect HR $\geq$ 50% base-line Day 9: Erect HR $\geq$ 50% base-line
	Placebo	#10	Day 10: Erect HR $\geq$ 50% base-line

rechallenge and he was continued at 75 mg. Three of ten subjects responded at 75 mg (all had transient increases in supine systolic blood pressure — including the responder at 50 mg). Three of six subjects responded at 150 mg and two of two subjects at 250 mg.

Peak Supine Blood Pressure Means: The average peak increases in supine blood pressure compared to placebo were transient and were not associated with peak PPA plasma levels; blood pressure decreased even as plasma levels remained elevated. Plasma levels remained elevated for four hours.

Peak increases in supine blood pressure for Regimen A (PPA) generally occurred 40 minutes to 1 hour after dosing. The average peak increases in supine blood pressure for PPA compared to placebo were 17/7 mm Hg at 50 mg, 24/7 mm Hg at 75 mg, 42/12 mm Hg at 150 mg and 78/32 mm Hg at 250 mg, suggesting that significant pressor responses to PPA are associated with single immediate release doses of 75 mg and higher. Peak increases in the active group as compared to placebo group peak were:

Dose (n)	Peak mm Hg Increases (All Subjects) PPA/Placebo
50 mg (10)	17/7
75 mg (10)	24/7
150 mg (6)	42/12
250 mg (2)	78/32

Peak increases over placebo in supine blood pressures of white vs. black subjects were:

Dose	Peak mm Hg Increases PPA/Placebo			
	White	(n)	Black	(n)
50 mg	7/7	(7)	42/3	(3)
75 mg	17/3	(7)	42/17	(3)
150 mg	42/12	(6)	not dosed	(0)
250 mg	78/32	(2)	not dosed	(0)

Data from Holter Monitoring showed there were no significant arrhythmias or changes in cardiac rate noted in the 24-hour Holter monitoring at any of the doses studied. Subject #7 (Regimen A), noted to have WPW Syndrome on placebo Day 3, had no Holter changes after administration of 50 mg and 75 mg PPA. However, this subject was discontinued from further study after placebo Day 9 because of retrospective concern about baseline Holter readings. Subject #8 (Regimen B; given placebo only) was noted to have possible sustained ventricular tachycardia events on placebo Day 3, had no events on Day 4, and was discontinued from further study after placebo Day 6 for the same reason.

Regarding PPA Blood Levels, levels of PPA in plasma were related to the dose administered. For each dose the mean peak plasma level of PPA (immediate release) was detected between one and two hours following dosing. Plasma levels of drug remained near peak values during the first 4 hours after dosing and decreased gradually from 4 to 8 hours. Since the pressor responses seen in the study were in all instances very transient there was no correlation between increased blood pressure and plasma levels of PPA.

Regarding Subjective Symptoms, the major subjective symptom reported on both Regimens A and B was headache (3 reports Regimen B placebo, 3 reports Regimen A placebo, 3 reports Regimen A active). Other symptoms reported included dizziness/light-headedness, palpitations/irregular heart rate, nausea and chest pain.

In conclusion, when ten normal male subjects were given a single dose of 50 mg PPA — twice a current recommended dose of 25 mg as a nasal decongestant — one (#12) experienced a pressor response.[2] This response was not reproduced on rechallenge.

_____

[2]   Note: Pressure responses, when they occurred, were usually greater when measured when the subjects were supine and unless otherwise noted, mention of pressure changes in this section will refer to the supine measurements.

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When the same ten subjects were given a single dose of 75 mg PPA —
three times a current recommended dose of 25 mg as a nasal
decongestant — the mean peak difference over placebo values was
24/7. Three subjects (#3, #12, #15) experienced significant
indicator responses, which were reproduced on rechallenge.

NOTE: Subjects #3, #12 and #15 were the only black subjects
included in group A. The mean peak increases over placebo at 50 mg
for these three subjects was 42/3 as compared to 7/7 for white
subjects. At 75 mg, mean peak increase over placebo was 42/17 as
compared to 17/3 for white subjects. These three subjects were not
included in further dosing.

Of the six subjects receiving 150 mg PPA, three (#1, #11, #14) had
significant increases in blood pressure. Subject #1 developed
postural hypotension 4 hours after dosing and was not
rechallenged. The pressor response in Subject #11 was reproduced
on rechallenge. Subject #14 was given Catapres (PO) 12 minutes
after his blood pressure was determined to be 194/104. Eleven
minutes after administration of Catapres his blood pressure was
164/98. Subject #14 was not rechallenged. The average peak
increase over placebo for subjects #1, #11 and #14 was 58/13, as
compared to 26/11 for the other three subjects dosed with 150 mg
PPA.

Of the remaining three subjects, one (#4) was discontinued from
further active dosing because of "off and on headaches" on the
placebo days prior to 250 mg.

Of the two subjects (#9, #10) receiving 250 mg, 10X the recommended
dose, both had significant indicator responses. Peak supine blood
pressure for #9 was 184/104 and 220/110 for #10. The mean peak
increase over placebo was 78/32.

There was no correlation between blood pressure response and plasma levels of PPA. When present, the pressor response was transient, lasting a matter of minutes, while plasma levels of PPA persisted at near peak values for more than 4 hours. This suggests a compensatory mechanism against the cardiovascular effects of PPA.

In summary, the objective of this study (20) was to determine the cardiovascular changes noted with oral administration of single immediate release doses of phenylpropanolamine HCl. The data showed an increased occurrence of pressor responses becoming significant with single doses $\geq$75 mg PPA.

These results are in agreement with observations of others (Reidenberg, 22) concerning the blood pressure, dose-response characteristics of PPA, indicating sustained increases in blood pressure in one-third of subjects receiving single oral doses of 85 mg or more. Reidenberg (22) reported dose response characteristics of PPA including transient increases in blood pressure of one-third of subjects dosed at 85 mg compared with only one-tenth of those dosed at 50 mg. These results indicate the dose of PPA associated with significant cardiovascular effects is at least three times the dose of PPA recommended by the FDA Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products (FR Vol. 44, No. 176, September 9, 1976, p. 38312).

However, the clinical significance of the transient elevations in blood pressure seen in the present study is not apparent. First, changes of similar magnitude were seen in subjects on placebo. Secondly, the normal 24-hour range of diastolic pressure variation has been determined by Pickering, et al. (23) and Harshfield, et al. (24) to be on the order of 46 mm Hg and 90 mm Hg between the highest and lowest diastolic and systolic blood pressures, respectively. The transient changes seen in this study are within this normal range.

C.   Schumann, P.R., et al.:   The Effects of immediate release
      phenylpropanolamine HCl on blood pressure.   CIBA Consumer
      Pharmaceuticals, Edison, NJ, 1988 (Reference 21)

In order to elucidate the effects of PPA on blood pressure and
heart rate, CIBA Consumer Pharmaceuticals conducted a rising dose
titration study. The protocol was prepared by CIBA and reviewed by
the Food and Drug Administration prior to initiation of the study.

The results of the CIBA study show:

a.   A direct correlation can be described for blood pressure,
      plasma concentration and oral dose of immediate release PPA.

b.   Clinically meaningful increases in blood pressure were not
      observed at immediate release doses of PPA less than 125 mg
      — 3.5 to 5 fold multiples of the maximal immediate release
      doses in OTC decongestant and weight control products in
      Canada and the U.S.

c.   The data on heart rate and blood pressure provide evidence
      for tachyphylaxis or tolerance to the blood pressure effects
      of repeated dosing with PPA.

Tables depicting the results and a full report of the study can be
found in Reference 21 of the Appendix.

Methods: Twelve healthy normotensive volunteers (5 females, 7
males; 2 blacks, 10 whites, mean age [± S.D.] 28 ± 6 years, mean
height 68 ± 3 inches, and mean weight 143 ± 20 pounds) completed a
single blind, rising, single-dose assessment of the effects of
immediate-release PPA on supine, seated, and standing systolic and
diastolic blood pressures and heart rate. After equilibration (10

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minutes supine, 3 minutes standing and 3 minutes seated), vital
sign measurements were made in quadruplicate in each position prior
to dosing and at 0.5, 1, 2, 3, 4, 5, 6, and 8 hours post-dosing
after placebo (twice prior to commencement of the PPA titration and
once at a randomly predetermined point during the dose titration)
and after PPA dosing (12.5, 25, 50, 75, 100, 125, and 150 mg). At
least 48 hours intervened between dosing periods. ECG's were
obtained prior to each dosing period and 2, 4, and 8 hours
post-dosing. Subjects were queried regarding symptoms throughout
the dosing periods. Blood was drawn for assay of PPA levels 1, 2,
3, and 4 hours after each test dose in each subject. Subjects were
dosed fasting and then received a standard breakfast and a standard
lunch 4 hours after the breakfast. Smoking was not permitted
during the study periods.

Subjects continued in the PPA titration according to specific
criteria and could be withdrawn for any of the following reasons:

a.   Subjects completed the highest (150 mg) dose;
b.   Subjects experienced increases in blood pressure or changes
            in heart rate meeting predetermined withdrawal criteria
            (systolic blood pressure in any position $\geq$180 mm Hg or
            $\geq$40 mm Hg above the respective pre-dosing level;
            diastolic blood pressure in any position $\geq$110 mm Hg or
            $\geq$30 mm Hg above the respective pre-dosing level; or
            heart rate $\geq$150 beats per minute or $\leq$45 beats per
            minute above the respective pre-dosing rate);
c.   Subject had vital sign changes that the investigator
            interpreted as indicating the withdrawal criteria would
            be met at the next dosing level;
d.   Subjects had post-dosing ECG abnormalities considered
            sufficient severity to preclude further dose
            escalation; or
e.   The investigator thought that the subject should be withdrawn
            from the study for any other reason.

The investigator could repeat a PPA dose in a subject if findings
on the first exposure were equivocal with regard to criteria for
withdrawal from the titration.

Results: Of 20 subjects originally screened for this study, 12 met
entry criteria. Among these 12, 5 completed the titration through
the 150 mg dose, and 7 (2 at 100 mg and 5 at 125 mg) met withdrawal
criteria pertaining to systolic blood pressure prior to completion
of the titration. No subject left the study for symptoms, an
adverse event or a clinical laboratory abnormality.

Table H summarizes the lowest doses at which small, transient
statistically significant, but not clinically meaningful, changes
in supine, seated, and standing blood pressures and heart rates
were noted. For details and graphic depictions of these findings
see the full text and tables and figures of Reference 21 in the
Appendix.

As stated, none of the changes noted in Table H were clinically
meaningful according to the definition set forth by Weintraub et
al. (1). Clinically meaningful changes occurred at immediate
release doses of 125 mg and above, which are associated with plasma
PPA concentrations that much in excess of those associated with
immediate release doses in currently marketed OTC decongestant
products and sustained release OTC weight control products.

Further with respect to systolic blood pressure, all but two of the
healthy volunteers who completed the study manifested increases in

The investigator could repeat a PPA dose in a subject if findings
on the first exposure were equivocal with regard to criteria for
withdrawal from the titration.

Results: Of 20 subjects originally screened for this study, 12 met
entry criteria. Among these 12, 5 completed the titration through
the 150 mg dose, and 7 (2 at 100 mg and 5 at 125 mg) met withdrawal
criteria pertaining to systolic blood pressure prior to completion
of the titration. No subject left the study for symptoms, an
adverse event or a clinical laboratory abnormality.

Table H summarizes the lowest doses at which small, transient
statistically significant, but not clinically meaningful, changes
in supine, seated, and standing blood pressures and heart rates
were noted. For details and graphic depictions of these findings
see the full text and tables and figures of Reference 21 in the
Appendix.

As stated, none of the changes noted in Table H were clinically
meaningful according to the definition set forth by Weintraub et
al. (1). Clinically meaningful changes occurred at immediate
release doses of 125 mg and above, which are associated with plasma
PPA concentrations that much in excess of those associated with
immediate release doses in currently marketed OTC decongestant
products and sustained release OTC weight control products.

Further with respect to systolic blood pressure, all but two of the
healthy volunteers who completed the study manifested increases in
systolic blood pressure ≥ 40 mm Hg at 100 mg (2 subjects) or 125 mm
(5 subjects) or 150 mg (3 subjects). The greatest mean increase in
systolic blood pressure was 29.4 mm Hg in the supine position at
three hours after the 150 mg dose. In the supine and seated
positions, PPA-induced changes in systolic blood pressure ceased
abruptly between four and five hours post-dosing, an effect most

TABLE H

The CIBA Study (Reference 21)

PPA DOSES AT WHICH SMALL, TRANSIENT, STATISTICALLY SIGNIFICANT, BUT NOT CLINICALLY MEANINGFUL, CHANGES IN BLOOD PRESSURE AND HEART RATE OCCUR

	BLOOD PRESSURE		
POSITION	SYSTOLIC	DIASTOLIC	HEART RATE
Supine	Increased 50 mg	Increased 100 mg	Decreased 100 mg
Seated	Increased 75 mg	Increased 100 mg	Decreased 100 mg
Standing	Increased 100 mg	Increased 150 mg	* ___

*No statistically significant changes were noted.

NOTE: For details and graphic depictions of these findings see the full text and tables and figures in Reference 21 of the Appendix.

obvious after the 125 mg and 150 mg doses. In the standing position, the maximum mean increase in systolic blood pressure was small, and abrupt changes between four and five hours were not evident. At the 150 mg dose, however, a very clear biphasic (early increase, late decrease to below baseline levels) pattern for change in standing systolic blood pressure was evident.

Diastolic blood pressure responses, though smaller in magnitude, generally were parallel to drug-induced changes in systolic blood pressure. Increases in diastolic blood pressure tended to plateau at the 125 mg and 150 mg doses. Maximum mean diastolic blood pressures in the supine, seated, and standing positions were: 20.7 mm Hg (three hours after 150 mg); 10.2 mg Hg (one hour after 125 mg and 150 mg); and 11.2 mm Hg (two hours after 150 mg). Only the 150 mg dose showed a trend toward a biphasic response similar to that seen for systolic blood pressure.

Heart rate responses in this study revealed a trend toward a dose-related, bradycardic response associated with — but temporally slightly right-shifted from — early post dosing blood pressure elevations. This pattern was most obvious for the supine heart rate results.

Regarding ECG changes, transient and premature atrial contractions in clinically non-threatening PR interval prolongations were infrequent, being seen in three subjects at high PPA doses. In no case did they result in withdrawal from the study. In the case of PR-interval prolongation, the response was position on PPA re-challenge and may be either a direct effect of very high doses of PPA or an indirect effect due to vagal activation from blood pressure increases.

Using a mathematical modeling technique, described in detail in Reference 21, to assess the relationship between percent change in

supine systolic blood pressure and PPA plasma levels, the CIBA investigators calculated that plasma PPA levels of 385-390 ng/ml would be needed to raise the supine systolic blood pressure 20 mm Hg over a baseline of 110 mm Hg and to raise the supine diastolic blood pressure 10 mm Hg over a baseline of 65 mm Hg. Thus, the CIBA researchers concluded:

> "PPA dose plasma level data from this trial indicate that a 125 mg oral immediate-release dose of PPA would be required to achieve (transiently) plasma PPA levels of 385-390 ng/ml."

The CIBA investigators also concluded:

> "Data generated in this trial indicate that blood pressure and heart rate responses to immediate-release doses of PPA are dependent on at least three variables: dose, interval after dosing and position at measurement. The sample sizes for this trial are too small to allow conclusions, or even meaningful speculation, about influences of age, race, sex, height or weight."

Further, they stated:

> "The results of the study provide strong support for the idea that although PPA can elevate both systolic blood pressure and diastolic blood pressure in all measurement positions, its blood pressure elevating effects are most prominant in the supine position and, both on the basis of direct observation and mathematical modeling, only become of potential clinical relevance at plasma PPA levels close to 400 ng/ml, a level usually only obtained in healthy volunteers with immediate-release oral doses of about 120 mg."

Thus, blood pressure elevations due to PPA occur in healthy subjects at doses that are well above the 25 - 37.5 mg dosages allowed OTC for nasal decongestant activity (e.g., in Canada) or for aiding weight loss (e.g., in the U.S.).

IV.   CORRECT IDENTIFICATION OF ISOMERS IS VITAL TO INTERPRETING
      THE LITERATURE RE: PPA'S SAFETY PROFILE

A.   <u>Minor Structural Changes on Chiral Carbons Can Cause Dramatic
      Pharmacologic Differences</u>

Phenylpropanolamine (± norephedrine; dl-norephedrine; PPA) is a
sympathomimetic agent, similar in structure, but different in
function, from amphetamine and ephedrine. PPA is used in over 100
over-the-counter (OTC) and prescription medicines with an average
of some 6 billion doses consumed each year (see Table A for PPA
products currently marketed).

Norephedrine contains two asymmetric (or chiral) carbons; thus four
separate isomers or two pairs of enantiomorphs, or mirror images,
exist for norephedrine (Table I; page 53a).

<u>Despite structural similarities, significant chemical, physical and
pharmacological differences exist between the four norephedrine
isomers and their racemetric mixtures</u>. Careful attention must be
paid as to whether proper identification and reporting of these
compounds in studies which describe their actions has been given.
In a number of instances such care was not given (31-36), and
confusion regarding PPA's safety resulted. Section IV.B. below
explains the errors made in these studies (References 31-36).

PPA is a raceme or a mixture of equal amounts of d-norephedrine and
l-norephedrine. These isomers are also described as (+)
norephedrine and (-) norephedrine with the d or (+) and l or (-)
referring to the isomers ability to rotate polarized light. PPA
has an optical rotation of zero due to the 50:50 mixture of d and l

isomers thus each isomer cancels out the others ability to rotate
polarized light. Currently, there is no apparent commercial use
for either norephedrine isomer alone; however, the d-form of the
second set of norephedrine enantimorphs (d-norpseudoephedrine) has
been marketed abroad (Europe, Mideast, Africa and possibly other
regions) as both an anorectic and as a stimulant. PPA (d,l-norephe-
drine), while chemically similar to d-norpseudoephedrine and
sharing appetite suppressant properties is not a stimulant, and PPA
is neither sold — nor is it used — for that purpose. This
example of structural differences in isomers (i.e., PPA vs.
d-norpseudoephedrine) demonstrates how minor physiochemical
differences can yield functional differences of major importance
pharmacologically (Moya-Hoff, 25).

Early published studies demonstrated pharmacologically distinct
effects of the various optical isomers of phenylisopropylamines,
such as norephedrine and norpseudoephedrine. Fairchild and Alles
(26) ranked such isomers according to the degree of drug-induced
locomotor activity in mice. With (+) amphetamine ranked as 1.0,
the compound that caused the most locomotor activity, the remaining
isomeric forms were ranked as follows:

|		
(+)	amphetamine	1.0
(-)	amphetamine	0.25
(+)	norpseudoephedrine	0.10
(-)	ephedrine	0.04
(-)	norpseudoephedrine	0.02
(-)	norephedrine	*
(+)	norephedrine	*
(-)	pseudoephedrine	*
(+)	pseudoephedrine	*
(+)	ephedrine	*

*Stimulation only occurs at lethal doses or near lethal doses.

Previous work in human subjects by Hofman et al. (27) also showed
(+) norpseudoephedrine was more potent than caffeine but less
potent than (+)-methamphetamine, and the racemic (±)-norpseudo-
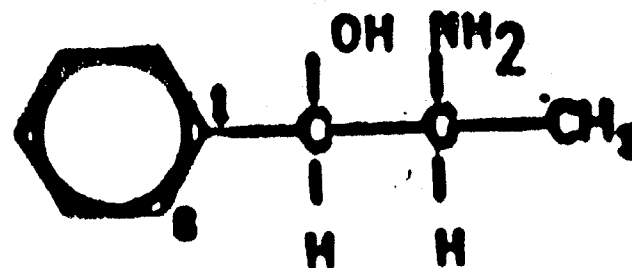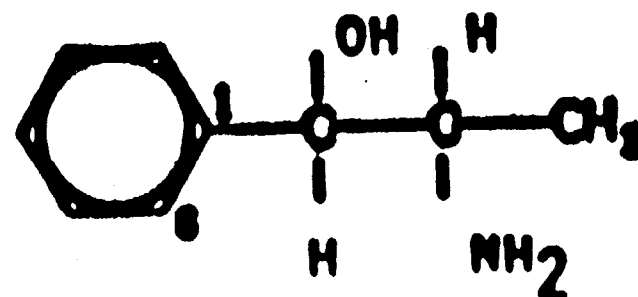ephedrine was a stronger CNS stimulant than (±)-ephedrine.
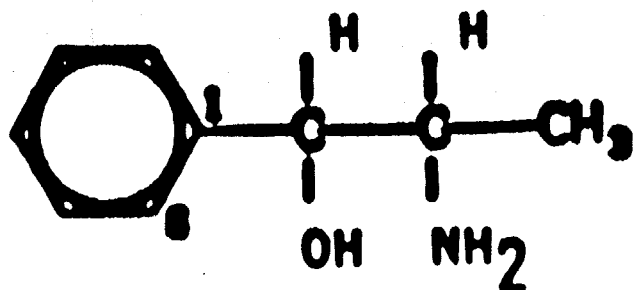
1-Norephedrine
Phenylpropanolamine
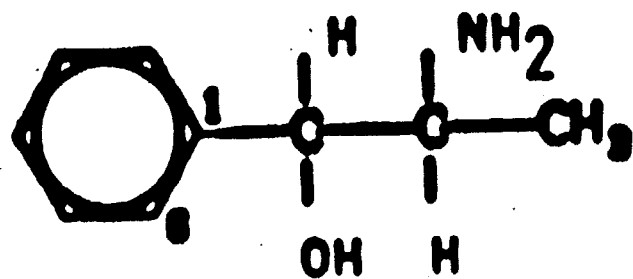
d-Norephedrine

1-Norpseudoephedrine

d-Norpseudoephedrine
(Trimolets)

TABLE I
- 53a -

The published research of Griffiths et al. (28) and Schuster and
Johanson (29) support the general conclusion that seemingly minor
configurational or structural differences due to chiral
(asymmetric) carbons can produce dramatic differences in
pharmacology. In these studies (±) norephedrine did not act as a
reinforcing agent on the basis of self injection in non-human
primates, while most anorexient phenylethylamines did.

More recently, Arch et al. (30) observed the following in
genetically obese and normal mice eating ad libitum or meal-fed:

1.   Only (±) norephedrine depressed weight over the 28-day study;
      (+) norpseudoephedrine was active only in early suppression
      of weight gain;

2.   (+)norpseudoephedrine more effectively increased energy
      expenditure in obese mice than (+) norephedrine;

3.   While (-) ephedrine and (+) pseudoephedrine were comparable
      in reducing lipid content in obese mice, (+)
      norpseudoephedrine was more active than other
      phenylisopropylamines in normal mice.

Therefore, unless formulations marketed in various countries are
identical with respect to the ratio and quantities of these
enantiomorphs, human ADR data and animal toxicological data on one
formulation should not be applied to safety analyses of other
formulations.

B.   <u>The Horowitz Study: The active ingredient originally identified in "Trimolets" as PPA was not PPA, so that the results of this and similar studies are of questionable relevance to the safety of PPA</u>

Beginning in 1978, a series of six articles (Frewin et al., 31; Horowitz et al., 32; King, 33; Lee et al., 34; Horowitz et al., 35; McEwan, 36) reported pressor effects in humans using Trimolets (an Australian diet aid) which was labeled [erroneously] as containing "phenylpropanolamine."

The results of Horowitz et al. studies (32, 35) have generated considerable anxiety about PPA's potential for vasoactivity, because Horowitz et al. depicted a drug with effects different from those seen with $\pm$ norephedrine (PPA), past and present. When considered on its face without critical evaluation, the results of the Horowitz study appeared dramatic with blood pressures up to 190/140 mm Hg requiring antihypertensive therapy in 4/37 healthy normotensive young volunteers within 2.5 hours or oral dosing and with 12 of the 37 subjects attaining a diastolic blood pressure greater than 100 mm Hg This study in conjunction with the other similar reports were instrumental in removing Trimolets from the Australian OTC market.

However, three features of the Horowitz study, which became known after publication of the study, show that the series of six papers reporting the Australian Trimolets experience were not actually reporting on the effects of PPA (Morgan, 37). First, Horowitz et al. only reported the ingredient in Trimolets as "85 mg of phenylpropanolamine per capsule," no further information being offered. Lee et al. (34) and Frewin et al. (31) described the ingredient in Trimolets as nonracemic mixtures -- "D-phenyl-propanolamine" and "d-phenylpropanolamine", respectively (Morgan, Reference 37, page 189-190). Chemical analysis of the product Trimolets purchased in 1984 demonstrated that more than one

phenethylamine may have been incorporated. Analysis demonstrated different Trimolets packages to contain the racemic form of norephedrine or d-pseudoephedrine, however, the actual content of Trimolets used by Horowitz was never clear and could have been racemic norephedrine, d-pseudoephedrine or d-norpseudoephedrine (Morgan 37). From a thorough follow-up with the Australian Proprietary Association and the investigators involved in the series of six studies pertaining to this issue, Morgan (37) concluded that Trimolets — because of the subjective symptoms noted in the 1980 Horowitz et al. (35) study — contained d-norpseudoephedrine.

Second, though advertised as a timed release preparation, Trimolets actually provided a "bolus" dose of 85 mg by releasing its active ingredient which was approximately 3.5 times more than the conventional 25 mg dose of PPA (Morgan, 37). Third, the results of the study by Horowitz et al. (35) have never been replicated. Similar blood pressure changes have not been seen at doses of PPA of 100 mg in either of the recent PPA dose response studies conducted in the United States (see Section II.F.).

From this analysis of the Trimolets confusion, Morgan (35) concluded:

> "This [the conclusion that the ingredient in Trimolets was d-norpseudoephedrine] probably explains why U.S. reports (Saltzman, Dolan, and Doyne 1983; Ekins and Spoerke 1983) generally have found (±)-phenylpropanolamine to be the relatively safe drug it was thought to be since its introduction in 1936." (Page 190 of Reference 37.)

In summary, confusion concerning the stereochemistry of isomers of PPA — particularly in Australia with the product Trimolets — has resulted in the U.S. compound, termed here phenylpropanolamine or d,l-norephedrine, being tainted unjustly with the adverse profile of a more vasoactive and centrally active isomer, d-norpseudo-ephedrine. The data presented below lend additional support for

the long recognized safety of PPA when used according to OTC label
instructions.

V. INDEPENDENT ANALYSES OF THE SAFETY PROFILE OF PPA

A. **Overview**

Four independent analyses of cardiovascular-related and CNS-related
side effects reported with PPA ingestion have been undertaken by
Morgan (59), Lasagna (60), Maher et al. (61), and Garvey (52).
These investigators reviewed the available data in the form of case
reports, published clinical trials, studies on poison control data
bases, and adverse reaction reports in FDA's Spontaneous Reporting
System. Each of these investigators concluded from their in-depth
analyses that PPA, taken at recommended doses and approved
formulations (i.e., formulations which in fact contain PPA and not
another isomer), is a safe drug for OTC use.

This section provides summaries of the findings of:

1. Morgan (59), on cardiovascular- and CNS-related adverse
   reports, Section V.B. below;

2. Lasagna (60), on cardiovascular- and CNS-related adverse
   reports, Section V.C. below;

3. Maher et al. (61), on CNS-related adverse reports, Section
   V.D. below; and

4. Garvey (52), on serious adverse reports from FDA's
   Spontaneous Reporting System, Section V.E. below.

(Next page, please)

B. **Morgan's Safety Analysis of PPA: Cardiovascular- and CNS-Related Reports (Reference 59).**

Morgan (59) concludes that:

> "In my opinion PPA certainly meets all of the
> appropriate criteria for over-the-counter
> medication. It should remain in the
> non-prescription marketplace because it is
> applied to conditions subject to correct
> self-diagnosis and when used as directed has
> minimal adverse effects." (Reference 59,
> page 86)

In a _citational analysis_ of the PPA-ADR literature, including 53 human safety studies, Morgan (59) concluded that a "bias" against PPA exists in the literature which is not warranted from a careful analysis of the fact. Morgan stated in this regard:

> "The pattern of citation would seem to
> support in part an accusation of bias. The
> exclusion of safety studies, the exclusion of
> papers contrasting amphetamine to PPA, the
> resurrection of the flawed Fazekas et al.
> article, the misapplication of the ideas in
> the Rumack et al. article and the use of an
> editorial (Blum) as often as any post-1970
> toxicity paper all point to a bias in which
> the desire to damn PPA exceeded the
> appropriate construction of the facts
> necessary to criticize it. This citational
> study and the preceding analysis of the
> non-probity of the 53 PPA-ADR papers leads me
> to conclude that increased exposure to PPA is
> not the explanation for the burst of critical
> papers." (Reference 59, page 80)

In Morgan's analysis of cardiovascular-related side effects associated with PPA, he provided the following summary (see also Reference 59:

> "A general summary of the cardiovascular
> reports follows and is listed in Table VIII.
> I read thirty-six reports, of which fifteen

were refereed. Thirty-two were case reports
and four described clinical trials, one uncon-
trolled. Excluding the clinical trial
volunteers, fifty-four patients were
described. Increased blood pressure was most
often noted (thirty-five of fifty-four
patients). Six patients reportedly
experienced cerebral hemorrhage and twelve
had disturbed cardiac rhythm. Two patients
had hemiparesis without apparent vascular
accident and three patients had seizures.
(There is some overlap here because some
patients manifested more than one adverse
clinical event.) Thirty-eight patients were
identified as females; twelve as males.
Despite the recent increase in marketed
diet-aid products, twenty-two patients
ingested cough-cold preparations, an equal
number used diet-aid products. Twelve of
these anorexiant-associated cases used a
formulation unavailable in the United States
(Trimolets) and now discontinued in
Australia. Three patients in the cardio-
vascular group ingested look-alikes. In only
three of the fifty-four patients was the
presence of PPA verified by analytical
laboratory testing, and two of these involved
massive overdoses. Although dosage informa-
tion was not always carefully presented,
fourteen patients had clearly consumed
overdoses. In other cases where dosage
appeared normal, twelve subjects had consumed
the discontinued high-dose immediate-release
product (Trimolets) or were affected by drug
interactions that may have magnified normal
dosage (8 patients). In only sixteen of
fifty-four cardiovascular patients were no
other drugs involved. Associated drugs were
often products with known cardiovascular
effects (anti-cholinergics, caffeine, other
phenethylamines). In most patients there was
no "rechallenge" because some form of
in-hospital treatment was given as the PPA
product was discontinued. The four
rechallenges involved Trimolets (two cases)
or drug combinations (two cases). Forty-six
patients apparently recovered completely. In
five individuals in this cardiovascular
grouping PPA ingestion was apparently
associated with fatality." (Reference 59,
pages 32 and 39)

Morgan (59 concluded PPA is a safe OTC drug and stated that:

> "Using the operational structure recommended by Hutchinson (1983), these reports lose much of their impact. The commonest event, increased blood pressure, may have been related to large doses of PPA in some reports, but it may well have been related to concurrently used drugs, diseases and conditions such as anxiety and flawed experimental design. Overdosage was commonly involved and if we classify Trimolets as a significantly high-dose product, the number of cases involving them plus the drug interactions indicate that actual overdose was involved in the great majority of reported cases. Despite the danger of uncritically accepting the patient's identification of PPA, it was analytically identified in body fluids in only three cases. Fortunately, nearly all patients recovered without sequelae and none of the five deaths can be unequivocally attributed to PPA." (Reference 59, page 50)

With respect to CNS stimulation reports, Morgan concluded:

> "The body of the above publications, using the operational definitions presented, is even more questionable than are the cardio-vascular cases. Most patients with anxiety or psychosis had consumed other drugs with CNS activity. Many had preexisting mental aberrations. Without Dietz's uncontrolled survey there are very few patients without described alternate etiologies. In the few instances where PPA's presence was verified, the interpretation is still clouded and there is a striking absence of the most important necessary data — prior history. Any interpretation is also affected by the continuing paucity of experimental proof that the drug has important CNS stimulating properties." (Reference 59, page 56)

C.   Lasagna's Safety Analysis of PPA: Cardiovascular- and CNS-Related
      Reports (Reference 60)

More recently, Lasagna (60) undertook an independent assessment of
PPA's safety profile. He concluded:

> ". . . although these few adverse drug
> reaction reports suggest that phenylpropanola-
> mine may cause adverse reactions, controlled
> clinical trials have repeatedly demonstrated
> that phenylpropanolamine, taken at recom-
> mended doses in approved formulations (which
> in fact contain phenylpropanolamine and not
> another isomer), is a safe drug. In safety
> studies specifically designed to test cardio-
> vascular and CNS effects, a total of more
> than 1000 patients were given phenylpropanola-
> mine at recommended doses; phenylpropanola-
> mine produced no significant adverse effects
> (these studies are reviewed later in this
> chapter). In addition, more than 50
> controlled clinical trials of the efficacy of
> phenylpropanolamine-containing products for
> use as nasal decongestants, appetite
> suppressants, or in treatment of urinary
> incontinence confirm the low incidence of
> side effects when phenylpropanolamine-con-
> taining product are taken in recommended
> doses (these studies are reviewed in Chapter
> 5). Furthermore, studies have shown that,
> even when taken at doses as high as 3 to 10
> times the recommended dose, phenylpropanola-
> mine produced no significant side effects
> (these studies are reviewed in this
> chapter). Finally, evaluation of overdose
> cases reported to a poison control center
> confirms the safety of phenylpropanolamine
> (Ekins and Spoerke, 1983)." (Reference 60,
> pages 192-193)

Lasagna further summarized his findings on cardiovascular-related
effects associated with reported PPA use as follows:

> "It appears that phenylpropanolamine, taken
> at recommended doses for up to 2 months, is

unlikely to produce significant cardio-
vascular toxicity. Even at higher-than-recom-
mended doses, sustained-release phenylpro-
panolamine formulations produced no
significant elevation of blood pressure.

Additional evidence regarding the cardio-
vascular toxicity of phenylpropanolamine
comes from case reports of adverse drug
reactions and overdoses. One-hundred-eight
such case reports have been published: 63
cases of adverse reactions and 45 overdose
cases. Most of these cases were reported
after 1965. Cardiovascular effects were
involved in 74/107 cases. These effects
ranged from subjective report of palpitations
and headache, to clinically confirmed
elevation of blood pressure with either
increased or decreased heart rate, cardiac
arrhythmia, cardiac arrest, or cerebro-
vascular hemorrhage. In acute adverse
reactions and overdoses, the dose of
phenylpropanolamine ranged from 25 to more
than 3000 mg; no relationship between the
dose and intensity of the cardiovascular
responses can be discerned. Undoubtedly,
some adverse reactions to phenylpropanolamine
at recommended doses were idiosyncratic
responses (i.e., rare and peculiar individual
reactions) such as may occur with any drug.
In addition, many of these cases involved
combination drug products and, therefore, it
is impossible to attribute the effects solely
to phenylpropanolamine (or any other of the
drugs in the formulation). Furthermore, in
most of the cases no tests were conducted to
confirm the presence of phenylpropanolamine
in blood or urine.

"In most of the cases, the cardiovascular
reactions were relatively mild and brief.
Most patients required no medical treatment,
and the symptoms resolved within a few hours.

"However, a few of the reported cardiovas-
cular adverse reactions and overdose effects
were severe. Thirteen cases of cerebrovas-
cular hemorrhage and nine fatalities have
been reported. Products containing

phenylpropanolamine alone were involved in
only three cases: One person had diabetes,
one was taking a prescription MAO inhibitor
for a preexisting psychiatric disturbance,
and one took an overdose (five appetite
suppressant capsules, dose not specified).
The other cases involved ingestion of
combination products (phenylpropanolamine and
caffeine, decongestant products, look-alike
stimulants; four cases each); thus the
toxicity cannot be attributed solely to
phenylpropanolamine. The dose of
phenylpropanolamine appears to be unrelated
to the clinical outcome in these cases. One
fatality occurred in a woman (a diabetic) who
reportedly took on 75-mg phenylpropanolamine
capsule a day for 2 days; at the other
extreme, in a suicide attempt one man took an
estimated 3000-3750 mg of phenylpropanolamine
plus pseudoephedrine and antihistamines,
developed an intracerebral hematoma, but
survived and recovered completely. These
examples demonstrate the extreme variability
in the case reports.

"Finally, the number of adverse drug reac-
tions and overdose cases must be balanced
against the total phenylpropanolamine consump-
tion by the general public. It has been
estimated that approximately 3-5 billion
doses of phenylpropanolamine are consumed
annually in the United States. By compari-
son, only 108 adverse reactions and overdose
cases have been reported in over 20 years.
It is impossible to estimate how many adverse
reactions are unreported. Nonetheless, the
number of adverse reactions must be a very
small fraction of the total number of doses
consumed.

"Thus, the results of extensive clinical
trials demonstrate that phenylpropanolamine
is unlikely to produce clinically significant
cardiovascular toxicity when administered at
recommended doses. In rare instances cardio-
vascular adverse reactions occur even at
recommended doses, and cardiovascular
reactions do occur in overdose cases."
(Reference 60, pages 289-291)

With respect to CNS related effects associated with PPA use, Lasagna (60) concluded:

"Compared to the extensive clinical studies of cardiovascular toxicity of phenylpropanolamine, fewer studies have tested the potential for CNS toxicity. Several large-scale clinical safety studies have been conducted to evaluate whether phenylpropanolamine changes affective state or mood, to determine the subjective rating of the drug effects, and to assess phenylpropanolamine's abuse liability. In these studies phenylpropanolamine has uniformly produced minimal CNS effects and very low abuse liability. Studies in experimental animals likewise demonstrate that phenylpropanolamine has very low abuse liability. Furthermore, the incidence of CNS side effects has been consistently low in extensive clinical efficacy studies.

"Of the 108 adverse drug reactions and overdose cases, 64 cases involved CNS effects. Most of the cases involved acute phenylpropanolamine ingestion at doses ranging from 25 to approximately 2500 mg. Most of the CNS reactions occurred at lower doses of phenylpropanolamine (usually 100 mg or less); the CNS toxicity appears to be unrelated to the dose ingested.

"The most frequently reported CNS effects were nervousness, hallucinations, psychotic episodes, and seizures. As with the cardiovascular toxicity, these effects usually were relatively brief. In most patients, the symptoms abated in a few hours without medical treatment. It should be noted that several of the patients had histories of psychiatric disturbance or drug abuse, suggesting that people with preexisting psychiatric or neurologic conditions may be predisposed to phenylpropanolamine-induced CNS reactions.

"Many of the adverse reactions and overdose cases involved combination products that contained other CNS-active drugs; caffeine,

ephedrine, antihistamines, or belladonna alkaloids. These components undoubtedly contribute to the reported CNS toxicity.

"Thus, clinical efficacy studies demonstrate that most individuals taking recommended doses of phenylpropanolamine experience no significant CNS stimulation; however, some individuals do have idiosyncratic responses. Furthermore, clinical safety studies demonstrate that phenylpropanolamine produces minimal CNS stimulation and has very low abuse potential. Analysis of the adverse drug reaction and overdose case reports reveals that phenylpropanolamine is associated with a low incidence of CNS stimulation. People with preexisting neurologic or psychiatric conditions may be at higher risk for phenylpropanolamine-related CNS toxicity." (Reference 60, page 292)

D. **Maher et al. Analysis of PPA: CNS-Related Reports (Reference 61)**

In a prepublication manuscript, Maher et al. reviewed CNS-related adverse effects reported to be associated with PPA. The following paragraphs are a restatement of the findings and conclusions of Maher et al. (61).

A concern expressed about PPA has been that it may produce mood modification and reinforcement, and thus may become a drug of abuse. However, a number of studies have documented the inability of PPA to cause significant mood modification or reinforcement. These include prospective studies of mood modifying substances, surveys of drug abusers under treatment, and reports from the U.S. federal government's vehicle for monitoring and tracking trends in drugs of abuse, the Drug Abuse Warning Network (DAWN).

Some have expressed the fear that PPA might be taken by drug abusers for the purposes of obtaining a "high" or otherwise modifying their mood. There was never any credible evidence that this was occurring but there have been occasional anecdotal reports on adolescents using "look-alikes" for purposes of mood modification (38, 39). Occasionally, PPA is mentioned in various publications as a drug subject to abuse, but without any documentation that it is actually being so used (40, 41).

The effect of PPA on mood inventories has been studied by a number of investigators of PPA. Bigelow et al. (42) employed the ARCI scales and found no statistically significant differences between PPA and placebo, after 25 mg t.i.d. or 75 mg controlled release QD doses. In a supplemental crossover design study with PPA and placebo, using visual analog and the ARCI scales, Bigelow et al. (42) found no amphetamine-like effects and no differences in subjective drug preferences, magnitude of effects, or type of effects.

The National Institute on Drug Abuse (NIDA) has sponsored annual surveys (43, 44) of substance abuse among high school seniors since 1975. Two years earlier, the Institute funded the first of a regular series of household surveys of substance abuse among American adults. Neither the high school nor the adult survey has ever reported PPA to be a drug of abuse.

If PPA were being taken by people who were attempting to modify their mood by drug use, such practices would certainly emerge from the records of treatment programs for drug abusers. Neither of the two major national data banks on drug abuse, the Drug Abuse Epidemiology Data Center (DAEDC) and the Client Oriented Data Acquisition Program (CODAP) reports PPA to be a product taken by drug abusers in treatment (45). So few PPA-positive urines emerge

from the testing of approximately 40,000 samples per month from participants in New York State drug abuse treatment programs that the State discontinued testing for PPA (46).

The DAWN data (47) derive from a national sample of 744 hospital emergency rooms and 75 medical examiner facilities, which report all episodes of the nonmedical use of a substance for psychic effect, dependence, or suicide attempts. The DAWN reports are issued semiannually. For the last several years, an average of approximately 1/10 of 1% of the total number of reported episodes involved PPA. During this period, PPA ranked, on the average, 114th in the incidence of substance reported to DAWN (47). It is not surprising that a commonly used agent such as PPA would be reported in drug misadventure. However, even these low levels of reporting are not necessarily associated with biological harm, although appearing in emergency room charts.

Similar findings derive from the experiences of the 57 poison control centers that report to the American Association of Poison Control Centers and service areas with 55 percent of the U.S. population. In recent years, PPA has annually accounted for an average of only 1/10 of 1% of the total number of cases reported to the centers (62, 63, 64, 65). By comparison, acetaminophen has averaged over 4% of the cases each year.

Another approach to the issue of the lack of drug abuse potential of PPA comes from the monthly counterculture publication High Times (48, 49, 50), which regularly evaluates drugs that can be used to provide a "high" or "rush," so that its readers who are psychoactive drug consumers may make "informed decisions" on what to buy. The magazine carried a three-part report on look-alikes and concluded that PPA did not contribute psychoactive, stimulant, or other mood modifying effects.

(Next page, please)

E. **Garvey's Analysis of Adverse Reactions to PPA (Reference 52)**

A detailed analysis of 333 serious putative adverse reactions associated with PPA use in the published literature and FDA Spontaneous Reporting System has been performed by Thomas Garvey, III, M.D. (President, Garvey Associates, Inc.) for CIBA Consumer Pharmaceuticals (52). This detailed analysis is presented in Reference 52. This analysis shows that the margin of safety for PPA is very wide -- with an estimated one serious adverse reaction per 250 million doses.

The analysis described in Reference 52 was undertaken to assess and quantify the risk of serious adverse reactions (e.g., death, cerebral hemorrhage, life-threatening hypertension) associated with appropriate use of recommended regimens of PPA (racemic norephedrine).

Published and unpublished case reports of adverse reactions associated with use of PPA were culled from the literature and from FDA's Spontaneous Reporting System, and collected, collated and analyzed. Only reports which describe "serious" reactions (i.e., involving an emergency room visit, prolonged outpatient observation, hospitalization, or death) have been considered in order to portray the most conservative position (52).

There are certain limitations to this database:

1. It is possible that some, perhaps many, of the reports analyzed here are duplications since it is not easy (or, in most cases, even possible) to determine with any certainty when data from FDA's Spontaneous Reporting System have been duplicated in published reports, nor when a published report includes a case described in yet another published report.

There is clearly some duplication in the Spontaneous
Reporting System data and discovered instances of such
duplication have been pointed out. Notwithstanding the
possible duplication of reports, it was assumed in Garvey's
analysis that, with the exception of obvious duplication,
each case has been reported only once — this is a
conservative assumption.

2. In general, important details regarding documentation of
    medication involved, dose, details of physical findings
    (e.g., blood pressure) and many other important data are
    often not available in these reports — those obtained
    through the Spontaneous Reporting System are notably
    deficient. Further, PPA blood levels are available in only a
    very few (n = 13) of the 333 cases analyzed.

    Available data describing drug name/type, dose concomitant
    medications (and doses if available), type and circumstances
    of adverse reaction, severity, treatment, outcome, patient
    age, sex, etc. were collected and collated and are summarized
    in Garvey's analysis (Reference 52).

3. Very few statistical analyses have been carried out on these
    data since information confirming the appropriateness of such
    analyses is largely lacking and the assumptions necessary to
    allow interpretation of such analyses are, in general,
    unjustified. Instead, the data can only be inspected and
    subjected to relatively simple analyses aimed at determining
    whether there is, in fact, risk of serious adverse reactions
    associated with use of recommended doses of PPA, what the
    magnitude of such risk is if it exists (obviously a very
    difficult question in the absence of reliable use data) and
    if such a risk exists, what the characteristics of the group
    of subjects at risk are.

Spontaneous ADR's were analyzed here in two discrete sets. One data set (230 cases -- Group A) includes cases culled from an exhaustive search of the published literature in English up to 1988 and all cases collected in FDA's Spontaneous Reporting System before October, 1983. A second data set (103 cases -- Group B) includes only cases collected in FDA's Spontaneous Reporting System between November, 1983 and October, 1987. The division of the ADR data into two sets is a practical consequence of the new availability of the more recent FDA Spontaneous Reporting System data after completion of the original analysis.

Group A, which includes cases from the published literature to 1988 and reports from the Spontaneous Reporting System collected prior to late 1983, comprises 230 cases of which 214 appeared in the published literature (66 of which are from one report of psychiatric disturbances reported in Sweden in a one year period -- Case A50) and 16 are derived from the Spontaneous Reporting System. These 16 cases of fatal or major medical consequences were selected from a total of 89 in FDA's Spontaneous Reporting System collected before 1983.

Group B Comprises 103 serious cases culled from a total of 279 in FDA's Spontaneous Reporting database for the period 1983-7.

The definition of "serious" for the 1983-7 included any case in which continued medical treatment appears to have been necessary -- a somewhat broader definition than was used for FDA cases collected prior to 1983. This definition was thought to reflect the types of cases reported in the published literature and it was further assumed that such a definition would give a more conservative estimate of the actual numbers of such cases.

Conclusions: Garvey (52) concluded that inferences about causal relationships between PPA and the various serious ADR's considered in his analysis cannot be easily drawn. In general, however, it is clear that a disproportionate number of the reported serious adverse reactions associated with PPA have occurred in subjects between 10 and 40 years of age (with most of these seen in subjects under 30) and that such reactions are far more common in females than in males, which is hardly surprising in light of the fact that most use of anorexic formulations of the drug is by women. Further, it is important to recognize that most of the cases have involved polypharmacy and/or excessive PPA doses, and that suicidal intent was often involved (at least 7 of the 19 deaths in Group A are said to have involved suicidal intent — relevant data are not available for the patients in Group B). Death following use of PPA alone in a recommended dose appears to be very, very rare, and the cases of the two deaths reported to be associated with PPA alone are subject to question due to inadequate collection of data.

Risk Estimation: Garvey (52) concludes his analysis with an estimation of the risk of serious adverse reactions associated with the use of PPA and concludes from this risk estimation that PPA is a safe OTC ingredient. A brief account of Garvey's risk estimation (52) follows.

If it is conservatively assumed that all of the 60 reactions in Groups A and B apparently associated with use of PPA alone (i.e., in the absence of concurrent use of other licit, illicit, or "recreational" drugs — e.g., alcohol) were in fact caused by the drug — and we do not know this assumption as fact — then at least some estimate of the risk of serious adverse reaction associated with use of PPA alone in a recommended regimen can be suggested. For this theoretical exercise, it seems appropriate (and easiest) to concentrate on the 19 cases of serious adverse reactions

associated with PPA monotherapy in any dose in Group B (which covers four years). Two other conservative assumptions must be made to allow this analysis:

About 5 billion doses of PPA are consumed each year in the U.S. (of which 75% are combination cough-cold products) as asserted by Morgan for the year 1984 (57) and it has been estimated that 9.5 million people use OTC weight loss products each year in the U.S. (an estimate for 1981) (58). Further assumptions are: (1) all adverse reactions associated with PPA monotherapy involved use of appetite suppressant formulations (i.e., all use of PPA for the cough and cold indication is in combination products and since FDA's 1981 and 1983 fiats, PPA appetite suppressant formulations cannot contain caffeine — the only other drug that had been regularly included with PPA in legal combinations); and (2) that most PPA use involved recommended doses of the drug. It should be kept in mind that some of the PPA-associated ADR's reported to FDA after 1983 almost surely involved illicit OTC look-alike combinations of PPA with caffeine or PPA with both caffeine and ephedrine, although it is not possible to identify such cases among the sparsely documented FDA reports.

On the basis of the very conservative assumptions above and the adverse reaction data for the period 1983-7 in FDA's Spontaneous Reporting System files the following conclusions can be reasonably supported:

1. Since only one death may have been associated with use of PPA alone in a recommended dose in the group of 103 serious cases culled from the total of 279 in FDA's Spontaneous Reporting System, the risk of this outcome with PPA monotherapy in a recommended regimen is 1 per 5×10^9 doses of PPA or about 1 per 10^7 (10 million) persons using PPA.

2.   The risk of any "serious" adverse reaction associated with use of PPA alone in any dose is about 1 per 2.5×10^8 PPA doses or about 1 per 5×10^5 users of PPA.

3.   Even if it is assumed that there is 50-fold under-reporting of adverse reactions with PPA (and this is an extremely conservative estimate) the risks of deaths or any serious adverse reaction associated with use of PPA alone appear to be very, very small.

These conclusions concerning the safety of PPA demonstrate a very wide margin of safety for PPA that is compatible with a general recognition of safety for this OTC ingredient.

Finally, and importantly, marketing exposure of PPA both OTC and Rx has been very wide for many years in Canada and the U.S. Frequent and/or serious adverse effects associated with the drug which might reasonably prompt action to limit risks seem very unlikely to have gone unnoticed, even in the face of under-reporting of adverse events. Hence, it seems reasonably to assume that serious adverse reactions associated with PPA in recommended doses occurs very rarely.

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