MEMORANDUM

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

DATE: APR 30 1991

FROM: Medical Officer, HFD-733

TO: Director, Division of OTC Drug Evaluation, HFD-210

THROUGH: Acting Director, Division of Epidemiology and Surveillance, HFD-730 4.30.91

SUBJECT: Epidemiologic review of phenylpropanolamine safety issues

## INTRODUCTION

This memo responds to your request for epidemiologic review of phenylpropanolamine (PPA) safety issues, particularly cerebrovascular accidents and hypertensive episodes reported in association with PPA ingestion.

The primary focus of this review is reporting of adverse drug experience (ADE) to the FDA Spontaneous Reporting System (SRS) and in the medical literature. Limitations of clinical trials and observational cohort studies for assessing PPA safety will also be considered.

Studies from Poison Control Centers and the Drug Abuse Warning Network[1],[2] will not be addressed in this memo because ADE reporting more specifically addresses the possibility of toxicity in individuals who have taken a drug. PCC and DAWN data reflect more on the availability of substances[3], and on trends in substance abuse[4], than on issues of drug toxicity and misuse amongst persons taking drugs for their intended effects.

When evaluating spontaneous reports, there is no single drug or drug group that is ideally suited for comparison with diet products containing PPA. Cough/cold products containing PPA usually include an antihistamine, antitussive, or other agent, and reporting patterns for these combination products may reflect in part the presence of non-PPA ingredients. In recognition of this limitation, spontaneous reporting of cerebrovascular accidents in association with PPA has been studied through three approaches: (1) review of all SRS CVA reports for PPA-diet and PPA-cough/cold drugs, (2) comparison of SRS CVA reporting for PPA-diet, PPA-cough/cold, and all other (non-PPA containing) drugs reported to the SRS and (3) review of all direct reports of CVA received by the SRS since 1977 to identify the most frequently suspected agents. As a final consideration, (4) the expected number of hemorrhagic CVAs in PPA-diet pill users on the first day of diet-pill use by chance alone has been estimated.

## METHODS

### (1) Review of SRS CVA reports for PPA-diet and PPA-cough/cold products

In the first approach, the Spontaneous Reporting System (SRS) was initially screened for all possible reports of cerebrovascular accident wherein a product containing PPA was listed as the suspect drug. The following costarts were used to identify possible cases of CVA: *cerebrovasc accid, cerebrovasc dis, emb carotid, emb cerebr, headache vasc, hem cerebr, hem intracran, hem subarachnoid, hemiplegia, infarct cerebr, occlus carotid, throm carotid, throm cerebr, and throm cerebr art.* Domestic spontaneous reports from health professionals only were included in this search; thus study, literature, foreign, and consumer reports were excluded. Reports solicited by a 1983 questionnaire from the Center for Science in the Public Interest were also excluded since they represent 'stimulated' rather than 'spontaneous' reporting. After this initial screen, possible CVA cases were manually reviewed to remove duplicate reports and to confirm that the reported diagnosis had been correctly coded. Reports of CVA were further classified according to whether the suspect product was a PPA-cough/cold, PPA-diet or *look-alike* agent. *Look-alike* drugs are illicit stimulants containing a variety of OTC ingredients including PPA, caffeine and others. Reports of adverse reactions associated with a *look-alike* product were excluded from analysis and will be summarized separately. Amongst CVA reports, the type of CVA was classified as hemorrhagic if the report specified *subarachnoid hemorrhage, intracerebral bleed,* bloody (nontraumatic LP) or xanthochromic CSF, or if CAT scan or autopsy results confirmed cerebral bleeding.

The age, sex, and year of reporting of the PPA-associated CVA cases defined the search criteria for identifying non-CVA reports in the SRS. The search criteria for all non-CVA reports was restricted to reports of women between the ages of 10-59 years that were received between 1977 and January 1991, since this reflected the age and sex distribution of the CVA cases.

Hypertensive reactions (without CVA) were selected as a second outcome of interest. Amongst the non-CVA reports, hypertension cases were identified by the reporter's impression of significantly elevated blood pressure.

### (2) Comparison of SRS CVA reporting for PPA-diet, PPA-cough/cold, and all other drugs

In the second analysis, the proportion of CVA reports among all direct adverse experience reports was calculated and compared for: (1) PPA-diet products, (2) PPA-cough/cold products and (3) all other (non-PPA) drugs reported to the SRS for women aged 10-59 years, from 1977 through January 1991. This was done by dividing the number of CVA reports by the total number of reports (for **all** adverse events) for each of the three drug categories. Direct reports, (i.e., reports mailed to the FDA by health professionals vs. the manufacturer), were used in this analysis to control for possible differences in individual manufacturer's reporting practices and for differences in reporting requirements for products covered by an NDA compared to those not covered. Calculation of these proportions used computer generated estimates of the number of CVA and non-CVA reports for each drug category. Computer generated frequencies were used for all three categories of products for this comparison only

because it was not feasible to screen the non-PPA, non-CVA reports manually for duplicates, due to the large number of reports involved. All other analyses on diet and cough/cold products reflect unduplicated manually reviewed reports.

Subsequent to the above analysis, all adverse event reports for PPA-diet and PPA-cough/cold drugs for women aged 10-59 years, from 1977 through January 1991, were manually reviewed and categorized according to type of adverse event. Adverse event-specific reporting proportions were calculated in the manner previously noted, by dividing the number of reports for each event by the total number of reports for that product. For example, the proportion of CVA reporting for PPA-diet drugs equalled the number of CVA reports divided by the total number of PPA-diet reports (with all reports having been manually reviewed). This proportion would have differed slightly from the proportion calculated with computer-generated frequencies because of removal of duplicate and miscoded reports. The proportions of CVA reporting were compared for PPA-diet and PPA-cough/cold drugs. To test the hypothesis of no difference in the CVA reporting proportions of PPA-diet and PPA-cough/cold drugs, a chi-square test of significance (two-tailed) was calculated. A Fisher's exact test was calculated when an expected cell value was less than 5.[5] In further analyses, odds ratios of the probability of CVA reports vs. other reports, for PPA-diet vs. PPA-cough/cold drugs were computed. Unlike a chi-square statistic, strata-specific odds ratios can be weighted and summarized to control for possible confounding variables, such as patient age, source of report, and year of report. For these analyses, possible confounding was controlled by a Mantel-Haenszel odds ratio[6] to adjust individually for each of these variables.

**(3) Review of all direct SRS CVA Reports since 1977**

In this analysis, all direct reports of CVA for women aged 10-59 years and received between 1977 and January 1991 were individually reviewed to exclude duplication and confirm the appropriateness of coding. The frequency of CVA by suspect drug category was then tabulated.

**(4) Estimation of the expected number of hemorrhagic CVAs in PPA-diet pill uses by chance**

The annual expected number of hemorrhagic CVAs in PPA-diet pill users on the first day of PPA-diet pill use, by chance, is the product of (a) the annual number of diet-pill users, (b) the annual incidence of hemorrhagic CVA, and (c) the probability of the hemorrhagic CVA occurring on any one day out of the year. The FDA does not have access to the marketing data of the annual number of new PPA-diet pill consumers; thus a literature estimate for the annual number of PPA-diet pill users has been used. It has been assumed that there are ten million PPA-diet users/year[8] and that the annual incidence of hemorrhage stroke is 1 event/10,000 person-years (table 8). The median length of a course of PPA-diet pills is assumed to be 16 days[7], although the expected number of first day events is not dependent on the length of the course.

### (5) Estimation of PPA-Product Use

Use of PPA-containing cough/cold and diet products was estimated from the U.S. Pharmaceutical Market - Drug Stores (USD) and Hospitals (USH). The USD projects national estimates of purchases by pharmacies from the paid invoices of a panel of almost 840 drug stores and a near census of wholesalers and chain warehouses. The USH projects national estimates of drug purchases by nonfederal acute care and psychiatric hospitals with data collected from a panel of 380 hospitals and a near census of wholesalers. An important limitation of this database is that the USD data does not represent sales of OTC drugs through supermarkets, mail-order or other unaudited channels and thus are liable to seriously underestimate total national sales. An underlying assumption in the use of these databases is that trends in purchasing of drugs are reflective of trends in general regardless of the type of outlet.

The National Disease and Therapeutic Index (NDTI) was used to estimate usage of PPA-cough/cold drugs by women, as a percentage of all PPA-cough/cold PPA "mentions". NDTI collects data from a panel of 2100 office-based private physicians, and "mentions" reflect a prescribed, recommended, or administered drug. Again, it is assumed that trends in the use of drugs by these physicians are reflective of trends in general.

## RESULTS

### (1) Review of SRS CVA reports for PPA-diet and PPA-cough/cold products

Twenty-nine domestic spontaneous reports of CVA with a PPA-containing product (excluding look-alikes) have been reported to the FDA since 1969, the beginning of the computerized reporting system (table 1). Nineteen cases (19/29 or 65.5%) were reported in association with a PPA-diet product, and ten (10/29 or 34.5%) with a PPA-cough/cold product. Amongst CVA reports with PPA-diet pills, 18/19 (94.7%) occurred in women. The ages of the 18 women ranged from 16-59 years, with a mean of 31.8 years (median 27 years). Only one PPA-diet pill case was reported in a man, aged 40 years (patient 13). Of the 10 reports of CVA with a PPA-cough/cold product, the patient was female in 7 cases (70%), and male in three cases (30%). The women ranged in age from 14-59 years, with a mean of 34 years (median 35). The two men wherein age was specified were 46 and 55 years. The type of stroke was hemorrhagic in 16/19 (84.2%) of reports associated with PPA-diet pills and 6/10 (60%) with PPA-cough/cold pills.

When duration of use was specified, the CVA occurred after the first dose in 9/17 (53%) instances for PPA-diet product reports, and in 7/9 (77.8%) in PPA-cough/cold product reports. The dose preceding the reaction exceeded the recommended dose of one capsule in 12/18 (66.7%) reports with PPA-diet products, and 4/9 (44.4%) with PPA-cough/cold products (in the 24 reports with dose specified). The time to onset of the CVA was specified in 6 cases of PPA-diet pill users as being 1 hour (1 report), 1-2 hours (1 report), 2 hours (2 report) and within 3 hours (2 reports) of the ingestion. Time to onset was noted in only 1 report of a PPA-cough/cold product as 12 hours. Concomitant medication (Nardil®) was implicated in 2/19 reports with PPA-diet products (10.5%) and 1/10 (10%) reports with PPA-cough/cold products. Other substances or medications which may have been factors were present in one case report

in a PPA-diet pill user (illicit substance abuse, patient 17) and in one case report of a PPA-cough/cold product user (oral contraceptive, patient 21). Two case reports with PPA-cough/cold products were potentially confounded by other explanations for the adverse event, specifically a recent radiocontrast procedure (patient 20), and history of a brain tumor (patient 23). Diagnosis of a CVA was confirmed by CAT scan, surgery and/or autopsy in 20 cases, and lumbar puncture in 2 of the remaining 9 cases. Two cases in PPA-diet pill users (2/19, 10.5%) and five cases in PPA-cough/cold users (5/10, 50%) had no documentation of radiological or anatomical (autopsy) evaluation. Documentation that aneurysm or arteriovenous malformation (AVM) was excluded as a predisposing factor by angiogram or autopsy was noted in 18/29 (62%) cases. Only one case, a PPA-cough/cold user, was found to have an AVM at surgery (patient 27).

Physicians were the reporting health professional in all but one instance (a PPA-cough/cold case). All PPA-diet cases were reported directly to the FDA in contrast to only 3/10 (30%) of PPA-cough/cold cases. The remaining seven were reported by the manufacturer, a difference which is likely ascribable to reporting requirements for manufacturers holding an NDA. A single physician reported 3 cases associated with PPA-diet pill use (patients 2,9,and 14) and one case with PPA-cough/cold use (patient 21). Another individual physician reported two cases in association with PPA-diet pill use (patients 8 and 10). All other cases came from unique reporters.

There were 7 reports of adverse reactions which occurred in women aged 10-59 years after having taken *look-alikes*. The specific reactions were stroke (1 report), seizure (1 report), and fatal overdose (5 reports).

**(2) Comparison of SRS CVA reporting for PPA-diet, PPA-cough/cold, and all other drugs**

CVA in women aged 10-59 years is an adverse event reported rarely in association with any drug, accounting for less than 1% of all direct or manufacturers' SRS reports for this age and sex group from 1977 through January 1991 (table 2). As noted previously, ADEs for PPA-diet products were reported directly almost exclusively. Although the data in Table 2 could not be verified by manual review because of the large number of direct non-CVA, non-PPA reports, the difference in CVA reporting proportions between PPA-containing and non-PPA containing products is striking.

In contrast to the rarity of overall SRS reporting of CVA for women aged 10-59 years amongst all drugs (<1%), CVA was the single most commonly reported event (18/51 reports, or 35.3%) for PPA-diet products, and represented 7/120 (5.8%) of all PPA-cough/cold ADEs (table 3). CVA cases were a significantly larger proportion of PPA-diet reports than of PPA-cough/cold products ($P < 0.001$) and adjusting individually for patient age, year and source of report did not alter the association. Table 4 shows the observed reporting frequencies for CVA, hypertension and all other adverse events, compared to the frequencies expected under the null hypothesis of no difference in reporting proportions by drug type.

Since adjustment of the number of CVA reports for total reporting (reporting proportions) could be influenced by the effects of non-PPA ingredients in PPA-cough/cold products, relative usage is another way to adjust the reporting frequencies. Reporting rates (the number of reports divided by the number of prescriptions for that drug) are commonly used to adjust the frequency

of reporting for drug use but can not be calculated for OTC drugs. Purchases of extended units (kilograms) of PPA-containing drugs were used as an index of relative use. Unadjusted for use, the ratio of PPA-diet to PPA-cough/cold CVA reports was 18:7 or 2.6 for women aged 10-59 years, from 1977 through January 1991; the ratio was considerably higher, 18:3 or 6:1 when only direct reports were considered. If PPA-diet and PPA-cough/cold drugs were used by women at the same rate, one would have expected a similar number of reports for each type of drug. Total kilogram purchases (both sexes) of PPA-containing products sold through drug, discount, and proprietary stores, and through hospitals are indicated in figure 1. The relative use of PPA-diet and PPA-cough/cold drugs is estimated to be approximately 1:1.8 -1:4.2. If one assumes that approximately 90% of all PPA-diet products[8] and 59% of PPA-cough/cold products[9] are used by women, the ratio of PPA-diet:PPA-cough/cold use is reduced to approximately 1:1.2 - 1:2.7 in women. Therefore, differences in use of PPA-diet and PPA-cough/cold drugs amongst women does not explain the higher frequency of reporting with PPA-diet products.

Hypertension (without stroke) was the second most commonly reported reaction amongst PPA-diet reports (9/51 or 17.6%). Amongst PPA-cough/cold reports, hypertension accounted for 9.2% (11/120) of all reports. When stroke reports were excluded from the denominator, the adjusted frequencies were 9/33 (27.3% of PPA-diet non-CVA reports) and 11/113 (9.7% of PPA-cough/cold non-CVA reports).

**(3) Review of all direct SRS CVA Reports since 1977**

When all direct CVA reports from health professionals were manually reviewed, the most frequently reported suspect drugs were PPA-containing diet products (table 5).

**(4) Estimation of the expected number of hemorrhagic CVAs in PPA-diet pill users by chance**

Table 6 shows a calculation of the annual number of hemorrhagic strokes in PPA-diet pill users that would be expected to occur by chance on the first day of PPA-diet pill use. Fewer than 3 cases/year of a hemorrhagic CVA on the first day of PPA-diet pill use would be expected to occur by chance alone (i.e., assuming that there is no association between PPA-diet pills and hemorrhagic CVA).

## DISCUSSION

There are several interesting features of the PPA-diet and PPA-cough/cold CVA reports, such as patient demographic characteristics and prior medical history, and the dose and duration of PPA-use. Young age and female gender were the primary demographic features of the reported patients; 10 of PPA-diet and 3 of PPA-cough/cold CVA reports were of women under the age of 30. The age and sex distribution of CVA reports is consistent with the expected usage of PPA-containing drugs.

Dose appeared to be a common risk factor for CVA independent of the type of PPA product. The dose exceeded labelled recommendations in two-thirds of CVAs associated with PPA-diet pill use and in slightly less than half of CVAs associated with PPA-cough/cold use.

This information suggests that exceeding the recommended dose may increase the risk of a CVA with any PPA-product. Stroke followed the first dose in half of PPA-diet pill cases and in over three-fourths of PPA-cough/cold cases, an observation which is consistent with tolerance to the pressor effects of PPA with repeated dosing.

Amongst CVA reports, predisposing factors were infrequently noted and the majority of patients had uncomplicated past medical histories. Concomitant medication or past medical history, when noted, (for example, MAO inhibitor use or hypertension) should be considered as a possible synergistic factor with PPA in addition to being considered as a potential "confounding" factor. Only two patients (of the nineteen reports with documentation of angiogram or autopsy) were found to have predisposing cerebral vascular abnormalities (AVM or aneurysm), making a causal association with the suspect PPA-drug more likely amongst the 17 patients with normal cerebral circulation.

Comparisons of spontaneously reported data between different drugs need to be cautiously interpreted in light of several potential sources of bias. Publicity in the lay and medical press may have influenced the reporting behavior of physicians confronted with an adverse event in a patient using a PPA-product. As an attempt to control for this bias, CVA reporting of PPA-diet products was compared to reporting of PPA-cough/cold products although this comparison would not have eliminated reporting bias if physicians had been more aware of safety issues with PPA-diet products than with PPA-cough/cold products.

Some differences in reporting were apparent between PPA-diet products and PPA-cold/cough products, most notably a higher volume of reporting with the latter. This higher volume may be due to the effects of antihistamine or antitussive agents in PPA-cough/cold combination products, or to differences in reporting requirements for PPA-cough/cold products covered by an NDA. 21 CFR 314.80 requires manufacturers of products with an NDA to report adverse events to the FDA.[10] No similar requirement exists for OTC drugs without an approved NDA, such as PPA-containing diet products. There were no CVA reports from the manufacturers of PPA-diet pills; in contrast 7/10 CVA cases with PPA-cough/cold products were reported by their manufacturers. This suggests that the number of direct PPA-diet CVA reports received by the FDA may be an underestimate of the number of reported CVA events.

Reports of non-CVA adverse events attributed to an antihistamine or antitussive agent in the PPA-cough/cold product could have lowered the CVA proportion of reporting amongst total adverse events. We were unable to stratify our results to control for confounding by combination ingredients because of the infrequent use of PPA as the sole cough/cold drug. As an alternative method to control for possible confounding, the number of CVA reports was adjusted for relative proportions of PPA-diet and PPA-cough/cold use in women. A higher frequency of CVA reporting with PPA-diet pills was noted regardless of whether total ADE reports or relative drug use was used as an adjustment factor.

When comparing adverse event reporting of two drugs, disparities in the initial year of marketing may be a potential source of bias because adverse events may be more frequently reported within the three years after initial marketing.[11] This consideration is an unlikely source of bias because both PPA-diet and PPA-cough/cold products were available in various forms prior to the inception of the current computerized SRS in 1969. Reporting of the two types of PPA-products was comparably distributed over the past decade and a half (figure 2b) thus the secular trend toward increased overall spontaneous reporting was excluded as a potential

bias. Figures 2a and 2b contrast the year of CVA with year of reporting to the FDA. The majority of events occurred and were reported during the years from 1981 to 1987. Five CVAs have been associated with PPA-diet pills since 1984 which is the year when caffeine was removed from PPA-diet pills.

The medical literature was reviewed to identify CVA reports associated with PPA-products (table 7). Reports submitted by non-North American authors were excluded from this table because different isomers or higher immediate release doses of PPA may be used in other parts of the world and their associated adverse events may differ from North American experience. CVA reports which had been submitted to the SRS[12],[13] and reports associated with *look-alike* products were also excluded. Thirteen North American published reports of stroke associated with PPA were identified; 10 reports followed use of a PPA-diet pill and 3 followed use of a PPA-cough/cold product. This observation is consistent with the larger number of SRS PPA-diet pill reports of CVA than SRS PPA-cough/cold product reports of CVA. The dose exceeded labelled recommendations in 8 cases. The CVA occurred after the first dose in 6/9 cases in which the author specified duration of use.

Since a similar dose of PPA is contained in many PPA-diet and sustained-release PPA-cough/cold products, different risks of CVA according to PPA-product type may seem to be an implausible hypothesis. Differences in the characteristics of PPA-diet pill users may offer one possible explanation for the higher frequency of CVA reporting observed with PPA-diet pills. PPA-diet pills users may be at higher risk of adverse drug events because of their potential for misuse of PPA-products. This hypothesis may explain in part why previous large studies have found no statistically significant association between PPA-cough/cold products and cerebral hemorrhage.[14],[15],[16] The relative risk of adverse outcomes in prescription PPA-cough/cold users was studied using Medicaid and Group Health Cooperative databases. The two studies found no association between PPA-cough/cold use and cerebral hemorrhage; these results are not unexpected and are consistent with our finding of only a small increase in the reporting frequency for CVA associated with PPA-cough/cold products when compared to overall CVA reporting for all non-PPA drugs in the SRS. In addition to possible differences in misuse potential between persons taking PPA-diet vs. PPA-cough/cold products, persons self-medicated with OTC products may differ from those taking medications on the advice of a physician. Further scientific research on this issue is necessary to test these hypotheses. National estimates of the prevalence of diet pill use and misuse, particularly amongst young women, are important areas for future research.

Another way to evaluate the association between PPA-diet pills and hemorrhagic stroke is to compare the observed number of reports of hemorrhagic stroke with the expected number based on the incidence of hemorrhagic stroke in young persons. Fewer than 3 hemorrhagic strokes/year would be expected to occur on the first day of PPA-diet pill use if there were no association between PPA-diet pills and hemorrhagic stroke. The expected number of cases would be further reduced if the population at risk, as suggested by the ADE reports, is a small percentage of all users who exceed the labelled recommendations. The expected number of cases would be further reduced if one assumes that the incidence of hemorrhagic stroke amongst women with normal cerebral circulation (that is, without a predisposing AVM or aneurysm) is lower than 1 event/10,000 person-years. While data on the latter two factors is not available, the number of expected cases based on coincidental exposure appears to be extremely small.

Fewer than 5% of all recognized ADEs are reported to the FDA.[17] Adverse events due to OTC agents may be even less likely to be reported due to lack of reporting requirements for drugs without an approved NDA, and a lower likelihood of inclusion of OTC products in drug histories. One would have to postulate unrealistically high rates of reporting with PPA-diet products to attribute the case reports of stroke to chance alone. In a circumstance analogous to the PPA-diet pill/cerebral hemorrhage issue, Inman and Vessey reported in 1968[18] on the controversy regarding oral contraceptives (OC) and thromboembolic deaths. The number of events expected by chance and the actual number of reports of thromboembolic deaths associated with OC was similar. The hypothesis of lack of association between OCs and thromboembolic disease was dependent on an assumption of virtually complete reporting of thromboembolic deaths. As one feature of their case-control study, they were able to determine that only 15% of thromboembolic deaths in women using OCs had been reported independently to the Committee on Safety of Drugs, despite a large amount of media publicity.

This analysis of reports to the SRS and in the literature suggests that PPA-diet pills increase the risk of CVA, although definitive hypothesis testing of this issue would be difficult. Clinical trials and observational cohort studies are unable to adequately test this hypothesis because of: (1) the required sample size and (2) the difficulty of exposure ascertainment.

The spontaneous rate of hemorrhagic stroke in the population of interest is a major determining factor in estimating the required sample size for a cohort study. Hemorrhagic stroke in young women is a rare event (table 8). Assuming an incidence of 10 events/100,000 person-years, a total sample size of 510,076 persons in a cohort study or clinical trial is necessary to have an 80% chance (power) of detecting a minimum relative risk of 2, at a significance level of $P < 0.05$.[19] Changing the assumption of incidence to 30 events/100,000 persons-years reduces the total sample size requirement to 169,976 persons.

A second obstacle to (observational) epidemiological studies of OTC agents is exposure ascertainment. Exposure to OTC products, particularly when taken without recommendation by a physician, will not ordinarily be recorded in automated databases.

Thus, while it is not feasible to test the hypothesis of an association between PPA-diet pills and cerebral hemorrhage by clinical trials or cohort studies, a case-control study of cerebral hemorrhage in young women is a possible approach. A prerequisite to the design of a case-control study and sample size calculation is an estimate of diet pill exposure in the population intended for study.

In conclusion, a number of lines of evidence from spontaneous reporting suggest that PPA-containing diet products increase the risk of CVA. While any one of these analyses has methodological limitations when considered alone, the analyses taken together are consistent in their implications. A case-control study of hemorrhagic stroke in young women would be the most feasible approach to test the hypothesis.

Please contact me if I can clarify any issues in this report, or if you wish to review the actual '1639' report forms or any cited references.

Heidi M. Jolson, M.D., M.P.H.
Epidemiology Branch
Division of Epidemiology and Surveillance
Office of Epidemiology and Biostatistics
443-2306

Concur:
Branch Chief: 4/25

CC:
HFD-100/Temple/Botstein
HFD-110/Lipicky/Dern
HFD-120/Leber/Laughren
HFD-150/Burke
HFD-700/Anello/Johnson
HFD-710/O'Neill
HFD-733/Stadel/Gross/Jolson/File chron, dru 1.7 phenylpropanolamine
HFD-735/Barash
HFD-737/Armstrong/Dreis

**Table 1. Demographic and clinical characteristics of patients with cerebrovascular accidents reported in association with PPA-containing products[1], to the Food and Drug Administration, from 1969 through January 1991[2].**

| # | Age<br>Sex<br>Year<br>Source | Suspect drug<br>Dose(capsules)<br>Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| **Reports associated with diet products containing PPA** | | | | | | | |
| 1 | 27<br>F<br>1977<br>Direct | Permathene-12[R]<br>1<br>One dose | Left hemiplegia; non-hemorrhagic | * | Nardil[R] | Clear CSF, normal bilateral carotid angiogram | Slight return of function |
| 2 | 19<br>F<br>1978<br>Direct | Dexatrim[R]<br>8 (50mg)<br>* | Intracerebral hemorrhage | "otherwise healthy" | * | Autopsy: normal vessels - no aneurysm or AVM | Death |

[1]Milligram content of product is indicated only when it was specified by reporter.

[2]Year refers to year of event.

* indicated incomplete information on the '1639' reporting form.

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 3 | 26<br>F<br>1981<br>Direct | Dexatrim[R]<br>2<br>One dose | Subarachnoid hemorrhage;<br>BP 200/100 | * | * | CSF (X2) 2000 RBCs all tubes, normal protein and glu, xanthochromia; normal bilat carotid and vertebral angiogram | Alive |
| 4 | 27<br>F<br>1981<br>Direct | Ayds[R]<br>3 (75mg)<br>one week at a dose of 1/day | Intracerebral hemorrhage 3 hours after dose | Wt 150-160 lbs, ht 63";<br>No history of hypertension; previously healthy | None | Bloody CSF; CAT scan- large left intracerebral hemorrhage. Autopsy: no congenital vascular malformations: toxicology: "phenylethylamine" in urine and caffeine in blood and urine, neg alcohol | Death |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 5 | 39<br>F<br>1981<br>Direct | Dexatrim[R]<br>"gradually increased dose"<br>2 weeks | Subarachnoid hemorrhage; BP 180/100 | * | None | CAT scan positive; "large amts of PPA recovered from blood and urine" | Death |
| 6 | 26<br>F<br>1982<br>Direct | Dietac[R]<br>2<br>One dose | lt hemiplegia; Basal ganglia hemorrhage 2 hrs after dose | None | None | CAT scan positive; angiogram - no AVM or aneurysm | Cran-iotomy; residual hemipleg-ia |
| 7 | 31<br>F<br>1982<br>Direct | Thinz[R] (25mg)<br>2 tabs taken 2hr apart<br>2 days | intracerebral hemorrhage in lt parieto-occipital area; BP 150/90 | None | None | CAT scan positive; angiogram - no AVM, aneurysm, or tumor | spastic hemipar-esis |
| 8 | 32<br>F<br>1982<br>Direct | Dexatrim[R]<br>2<br>* | Intracranial bleed with hypertension | 120 lbs., ht 61" | None | CAT scan; cerebral angiogram | Alive |
| 9 | 45<br>F<br>1982<br>Direct | Dexatrim[R]<br>2 (75mg)<br>1 dose | Intracerebral hemorrhage | Healthy | Nardil[R], prn Valium[R] | CAT scan - hemorrhage; autopsy with normal vessels, no aneurysm or AVM | Death |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 10 | 47<br>F<br>1982<br>Direct | Dexatrim[R]<br>1<br>4 days | Intracranial bleed with hypertension | 180 lbs., ht 63" hypertension off antihyper-tensives | None | LP, CAT scan, cerebral angiogram | Alive |
| 11 | 56<br>F<br>1983<br>Direct | Thera-Trim[R]<br>(75mg)<br>2<br>first dose | Bilat intracerebral hemorrhage; BP 140/100 | None | None | CAT scan positive | Recovery |
| 12 | 32<br>F<br>1982<br>Direct | Dexatrim[R]<br>"as directed"<br>4 days | Occipital stroke causing rt quadrantanop-sia | 15 pack-years smoking; toxemia with first pregnancy | * | "neurologic examination and testing" | Recovery |
| 13 | 40<br>M<br>1984<br>Direct | Dexatrim[R]<br>1<br>1 year | Rt temporal lobe infarct | 5-6 cigars/d, otherwise "no other cardiovascular risk factors" | None | * | Residual lt arm weakness and lt central 7th |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 14 | 59<br>F<br>1984<br>Direct | Dexatrim®<br>1 (75mg)<br>"chronic" | Intracerebral hemorrhage | Hydrocephalus-1970 (stable) | None | CSF "bloody", CAT scan - hemorrhage, Agram-beading, no AVM or aneurysm | Alive with disability |
| 15 | 16<br>F<br>1986<br>Direct | Dexatrim®, Acutrim II®<br>(mixture)<br>12<br>6 weeks | lt hemiparesis and homonymous hemianopia; intraparen-chymal hematoma and BP 172/108 within 3 hours of dose | 134 lb., ht 66" | None | CAT scan - rt posterior parietal intraparenchymal hematoma with mild mass effect | Alive with sequelae |
| 16 | 20<br>F<br>1986<br>Direct | Dexatrim®<br>6<br>1 dose | rt hemiparesis, lt parietal hematoma | * | None | CAT scan - lt parietal hematoma; cerebral angiography negative | Alive with disability |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 17 | 22<br>F<br>1986<br>Direct | Dexatrim[R]<br>2<br>1 dose | Rt frontal parietal hemorrhage 1-2 hours after dose | Cocaine used 3 weeks prior | alcohol, marijuana | CAT scan - hemorrhage; cerebral angiography negative | Alive |
| 18 | 23<br>F<br>1987<br>Direct | Dexatrim ES plus vit C[R] (75mg)<br>4<br>1 dose | Intracerebral hemorrhage | None | None | CAT scan; 4 vessel angiogram | Alive with sequelae |
| 19 | 25<br>F<br>1987<br>Direct | Dexatrim[R]<br>2<br>1 dose | Subarachnoid hemorrhage 2 hours after ingestion | 2 weeks post-partum | * | Bloody CSF; CAT scan - subarachnoid blood; normal angiogram X2 | Alive |
| **Reports associated with cold/cough products containing PPA** | | | | | | | |
| 20 | *<br>M<br>1974<br>Manuf | Ornade[R]<br>1 bid<br>2-3 days | Stroke following vertebral artery angiogram, 12 hours after dose | * | * | * | * |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 21 | 23<br>F<br>1981<br>Direct | Comtrex[R]<br>2<br>1 day | Intracerebral hemorrhage, rt hemiparesis | * | BCP | CAT scan - intracerebral hemorrhage, angiogram-beading, normal on repeat 1 month later; normal ESR, ANA, SPEP | Good recovery |
| 22 | 55<br>M<br>1982<br>Manuf | Ornade[R]<br>1 bid<br>3 days | Stroke causing rt sided partial paralysis | Hypertension | Dyazide[R], Keflex[R], Aristocort[R] | CAT scan - cerebral infarct, EEG and cerebral angiogram normal except 1 or 2 small aneurysms but no bleeding. | Returned to work |
| 23 | 39<br>F<br>1984<br>Manuf | Dimetapp[R]<br>1<br>1 dose | Brain hemorrhage | Brain tumor removed 3 years prior | None | * | Alive |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age Sex Year Source | Suspect drug Dose(capsules) Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 24 | 14<br>F<br>1984<br>Direct | Coricidin[R]<br>11<br>1 dose | Deep capsular infarct with lt hemiplegia | previous suicide attempt with OTC decongestant | None | Normal CAT scan and agram initially; at 1 week deep capsular infarct on CT; drug screen positive for PPA, chlorpheniramine, and ASA (non-toxic) | Alive |
| 25 | 50<br>F<br>1985<br>Manuf | Contac[R]<br>1<br>1 dose | Intracranial hemorrhage | depression | Nardil[R] | * | Alive with residual cognitive deficit |
| 26 | 59<br>F<br>1986<br>Manuf | Ornade[R]<br>*<br>* | Subarachnoid hemorrhage | 143 lbs, ht 66" | * | Urine PPA level 156 ng/l (therapeutic range) | Death |
| 27 | 46<br>M<br>1988<br>Manuf | Tavist-D[R]<br>1<br>1 dose | Subarachnoid bleed due to AVM; BP 160/80 from baseline of 90/60 | None | None | Surgery | Recovered with residual effects |

Table 1 (cont.) Characteristics of CVA cases reported with PPA

| # | Age<br>Sex<br>Year<br>Source | Suspect drug<br>Dose(capsules)<br>Duration | Symptoms and type of CVA | Past medical history | Concomitant medications | Evaluation | Outcome |
|---|---|---|---|---|---|---|---|
| 28 | 35<br>F<br>1989<br>Manuf | Tavist-D[R]<br>more than 10<br>1 dose | CVA | * | * | serum PPA level:<br>1090 ng/ml | Death |
| 29 | 17<br>F<br>1990<br>Direct | Contac [R]<br>6<br>1 dose | Intracerebral hemorrhage | * | None | Autopsy: massive intracerebral hemorrhage | Death |

ppacases.tab

Table 2. Computer generated frequencies of domestic spontaneous reporting[1] of CVA and all other adverse drug experiences which occurred in women aged 10-59 years, from 1977 through January 1991, according to phenylpropanolamine presence in product and source of report.

*Direct Reports*

| Product | Adverse event | | |
|---|---|---|---|
| | CVA[2] (%) | Non-CVA (%) | Total |
| **PPA-Diet** | 20 (40.8) | 29 (59.2) | 49 |
| **PPA-Cough/cold** | 4 (5.7) | 66 (94.3) | 70 |
| **All non-PPA** | 78 (0.5) | 14168 (99.5) | 14246 |
| **Total** | 102 (0.7) | 14263 (99.3) | 14365 |

*Manufacturer Reports*

| Product | Adverse event | | |
|---|---|---|---|
| | CVA (%) | Non-CVA (%) | Total |
| **PPA-Diet** | 0 (0) | 3 (100) | 3 |
| **PPA-Cough/cold** | 4 (5.1) | 74 (94.9) | 78 |
| **All non-PPA** | 643 (0.9) | 72799 (99.1) | 73442 |
| **Total** | 647 (0.9) | 72876 (99.1) | 73523 |

[1]Duplications were not excluded and the appropriateness of costart terminology was not confirmed for this table due to sample size considerations.
[2]CVA denotes cerebrovascular accident.

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Table 3. Frequency, type and severity of all adverse drug experiences associated with phenylpropanolamine-containing products, in women aged 10-59 years, reported to the FDA Spontaneous Reporting System, from 1977 through January 1991.

| Adverse event | Type of PPA-containing product | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cough/cold | | | | Diet | | | |
| | Severity | | Total | | Severity | | Total | |
| | Fatal | Non-fatal | N | % | Fatal | Non-fatal | N | % |
| **Allergic** | **1** | **23** | **24** | **20.1** | **-** | **1** | **1** | **2.0** |
| Anaphylaxis. | 1 | 4 | 5 | 4.2 | - | - | - | - |
| Arthralgia | - | 3 | 3 | 2.5 | - | - | - | - |
| Rash | - | 11 | 11 | 9.2 | - | - | - | - |
| Urticaria | - | 5 | 5 | 4.2 | - | 1 | 1 | 2.0 |
| **Cardiovascular** | **1** | **17** | **18** | **15.0** | **-** | **12** | **12** | **23.5** |
| Arrhythmia | 1 | 4 | 5 | 4.2 | - | 3 | 3 | 5.9 |
| Cyanosis | - | 1 | 1 | 0.8 | - | - | - | - |
| Hypertension | - | 11 | 11 | 9.2 | - | 9 | 9 | 17.6 |
| Myocardial injury/infarction | - | 1 | 1 | 0.8 | - | - | - | - |
| **Gastrointestinal** | **1** | **7** | **8** | **6.6** | **-** | **1** | **1** | **2.0** |
| Gastritis | - | 1 | 1 | 0.8 | - | - | - | - |
| Pancreatitis | - | - | - | - | - | 1 | 1 | 2.0 |
| Perforation | - | 1 | 1 | 0.8 | - | - | - | - |
| Vomiting and/or diarrhea | - | 4 | 4 | 3.3 | - | - | - | - |
| Other | 1 | 1 | 2 | 1.7 | - | - | - | - |

Table 3. (cont.) Frequency of all adverse drug events associated with PPA

| Adverse event | Type of PPA-containing product | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cough/cold | | | | Diet | | | |
| | Severity | | Total | | Severity | | Total | |
| | Fatal | Non-fatal | N | % | Fatal | Non-fatal | N | % |
| **Neurological** | **3** | **38** | **41** | **34.1** | **4** | **17** | **21** | **49.0** |
| Cerebrovascular accident | 3 | 4 | 7 | 5.8 | 4 | 14 | 18 | 35.3 |
| Headache | - | 4 | 4 | 3.3 | - | 2 | 2 | 3.9 |
| Lethargy | - | 6 | 6 | 5.0 | - | - | - | - |
| Mental status depression or coma | - | 6 | 6 | 5.0 | - | 2 | 2 | 3.9 |
| Paresthesia | - | 5 | 5 | 4.2 | - | 1 | 1 | 2.0 |
| Seizure | - | 5 | 5 | 4.2 | - | 2 | 2 | 3.9 |
| Syncope | - | 4 | 4 | 3.3 | - | - | - | - |
| Other | - | 4 | 4 | 3.3 | - | - | - | - |
| **Ophthalmic** | **-** | **5** | **5** | **4.1** | **-** | **1** | **1** | **2.0** |
| Amaurosis fugax | - | 1 | 1 | 0.8 | - | - | - | - |
| Diplopia | - | 1 | 1 | 0.8 | - | - | - | - |
| Iritis | - | - | - | - | - | 1 | 1 | 2.0 |
| Visual acuity | - | 1 | 1 | 0.8 | - | - | - | - |
| Other | - | 2 | 2 | 1.7 | - | - | - | - |

Table 3. (cont.) Frequency of all adverse drug events associated with PPA

| Adverse event | Type of PPA-containing product | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cough/cold | | | | Diet | | | |
| | Severity | | Total | | Severity | | Total | |
| | Fatal | Non-fatal | N | % | Fatal | Non-fatal | N | % |
| **Psychiatric** | - | **13** | **13** | **10.7** | - | **7** | **7** | **13.8** |
| Addiction | - | 1 | 1 | 0.8 | - | 1 | 1 | 2.0 |
| Aggitation | - | 2 | 2 | 1.7 | - | - | - | - |
| Anxiety | - | 1 | 1 | 0.8 | - | - | - | - |
| Depression | - | - | - | - | - | 2 | 2 | 3.9 |
| Emotional lability | - | 1 | 1 | 0.8 | - | - | - | - |
| Hallucination | - | 1 | 1 | 0.8 | - | 1 | 1 | 2.0 |
| Mania | - | - | - | - | - | 2 | 2 | 3.9 |
| Nervousness NOS | - | 7 | 7 | 5.8 | - | 1 | 1 | 2.0 |
| **Urological** | - | **3** | **3** | **2.5** | - | **1** | **1** | **2.0** |
| Frequency | - | 1 | 1 | 0.8 | - | - | - | - |
| Retention | - | 2 | 2 | 1.7 | - | 1 | 1 | 2.0 |
| **Other** | - | **8** | **8** | **6.7** | **3** | - | **3** | **5.9** |
| **Total** | **6** | **114** | **120** | **100** | **7** | **44** | **51** | **100** |

alladr.tab

Table 4. Observed and expected frequencies of cerebrovascular accident, hypertension, and other reporting for PPA-containing diet and cough/cold products under the null hypothesis of no difference in SRS reporting patterns by product, for women aged 10-59 years, from 1977 through January 1991.

| Observed Frequencies of Reporting | | | | |
|---|---|---|---|---|
| **Product** | **CVA[1]** | **Htn[2]** | **Other** | **Total** |
| **PPA-diet** | 18 | 9 | 24 | 51 |
| **PPA-cough/cold** | 7 | 11 | 102 | 120 |
| **Total** | 25 | 20 | 126 | 171 |

| Expected Frequencies of Reporting | | | | |
|---|---|---|---|---|
| **Product** | **CVA** | **Htn** | **Other** | **Total** |
| **PPA-diet** | 7 | 6 | 38 | 51 |
| **PPA-cough/cold** | 18 | 14 | 88 | 120 |
| **Total** | 25 | 20 | 126 | 171 |

[1] CVA denotes cerebrovascular accident.
[2] Htn denotes hypertension.

ppaexpec.tab

Table 5. Direct, domestic spontaneous reports[1] of cerebrovascular accidents in women aged 10-59 years received by the FDA, from 1977 through January 1991, according to suspect drug category.

| Product Category | Number of reports | % of total reports |
|---|---|---|
| PPA-diet[2] | 19 | 26% |
| Oral contraceptive | 15 | 20% |
| Thrombolytic agent[3] | 7 | 10% |
| Lactation suppressive[4] | 6 | 8% |
| Chemotherapeutic[5] | 5 | 7% |
| Radiocontrast[6] | 4 | 5% |
| Anticoagulant[7] | 3 | 4% |
| PPA-cough/cold[2] | 3 | 4% |
| Miscellaneous[8] | 11 | 15% |
| Total direct reports | 73 | 100% |

[1]Duplicate reports were excluded from frequency counts. Reports were individually reviewed to confirm appropriateness of diagnosis. Direct reports from health professionals only were included.

[2]See table 1 for specific product identities.

[3]Suspect products were Urokinase[R], Streptokinase[R], and Activase[R].

[4]All reports refer to Parlodel[R] (bromocriptine).

[5]Multiple chemotherapeutic agents were reported, including Nolvadex[R] (tamoxifen).

[6]Suspect agents included Hexabrix[R], Isovue[R], and Pantopaque[R].

[7]Suspect agents included heparin and warfarin.

[8]The following products were each reported once: unspecified diet pill, Provera[R] (medroxyprogesterone acetate), Zantac[R] (ranitidine), Chymopapain, DDAVP[R] (desmopressin acetate), glycerin, Accutane[R] (isotretinoin), oxytocin, Parnate[R] (tranylcypromine sulfate), Clomipramine[R] (anafranil), and pseudoephedrine.

Table 6. Calculation of the expected number of hemorrhagic strokes in PPA-diet pill users on the first day of PPA-diet pill use, due to chance.

1. In a population of 10,000,000 persons[1] with an annual incidence of hemorrhagic stroke[2] of 1 event/10,000 person-years, a total of 1000 hemorrhagic strokes/year would be expected to occur.

(10,000,000 persons)(1 stroke/10,000 person-years) = 1000 strokes/year.

2. If each of the 10,000,000 persons took diet pills anytime during a given year, and the average course of diet pill use lasted for 16 days, then 44 hemorrhagic strokes/year would occur by chance during any day of a 16 day course[3] of diet pills.

(10,000,000 persons)(1 stroke/10,000 person-years)(16 days/365 days) = 44 strokes/year.

3. The probability of a chance stroke on the first day of 16 days of diet pill use is 1/16. The annual number of expected strokes on the first day of diet pill use amongst 10,000,000 users is 2.7 cases/year.

(10,000,000 persons)(1 stroke/10,000 person-years)(16 days/365 days)(1 day/16 days)
= 2.7 strokes/year.

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[1]See reference number 8.

[2]See table 8.

[3]See reference number 7.

Table 7. Literature adverse experience reports of stroke associated with phenylpropanolamine[1] ingestion which were not reported to Spontaneous Reporting System, FDA. (U.S. reports only)

| Reference Year | Age/Sex | Product[2] Indication | No. tablets Duration of use | Time to onset | Reaction | BP response | Cerebral vasculature |
|---|---|---|---|---|---|---|---|
| [20] 1982 | 18/F | Comtrex® cold | 2 tablets * | 2.5 hours | subarachnoid and intravent hemorrhage | 210/130 | normal |
| [21] 1983 | 24/M | Dexatrim® (50mg) Diet | 8-10 tablets 3 months | * | lt frontal parietal infarct | * | normal |
| [22] 1984 | 25/M | * Diet | "five times the recom-mended dose" * | 0.5 hours | Subarachnoid hemorrhage | 180/120 | normal |
| [23] 1984 | 24/M | Danbade® (75mg) Cold | 40-50 Danbade® and 20 Drixoral® * | 2 hours | lt frontoparietal intracerebral hematoma with mass effect | 182/96 | normal |
| [24] 1985 | 20/F | Dexatrim® Diet | 2 tablets 6 months | * | rt frontal intracerebral hemorrhage | 210/130 | abnormal - arterial narrowing |
| 85 | 45/F | Dexatrim® (50mg) Diet | 1 tablet none in months | 1 hour | subarachnoid hemorrhage | 120/80 | normal |
| [25] 1987 | 20/F | * (75mg) Diet | 1 tablet none in 6 mo | "shortly after" | lacunar infarct of lt internal capsule | 130/70 | normal |
| [26] 1987 | 35/F | Dexatrim ES® (75mg) Diet | 1 tablet none in mo | 1.5 hours | rt frontal intracerebral hemorrhage | * | vasculitis |
| [27] 1987 | 27/M | Entex® (45mg) Cold | 13 tablets * | 1 hour | rt lenticular hemorrhage | 210/110 | segmental narrowing and dilatation |
| [28] 1987 | 39/F | Dexatrim® (75mg) Diet | 1 tablet first dose | 2-3 hours | rt putaminal hemorrhage and bilateral hematomas in the frontal poles | 160/104 | multifocal beading |
| | 32/M | Dexatrim ES® Diet | two tablets first dose | 8 hours | rt putaminal-capsular hemorrhage | 130/90 | normal |

Table 7. Literature review of stroke associated with PPA

| Reference Year | Age/Sex | Product[2] Indication | No. tablets Duration of use | Time to onset | Reaction | BP response | Cerebral vasculature |
|---|---|---|---|---|---|---|---|
| [29] 1987 | 30/F | Dexatrim ES® Diet | one tablet none in 10 mo | 0.5 hours | intra-axial hematoma with subarachnoid extension | 110/80 | diffuse beading |
| [30] 1989 | 17/F | Diet-Aid® (75mg) Diet | 5 tablets intermittently for 1 mo | 3-5 hours | rt parieto-occipital hemorrhage | 90/50 | beading |

[1]Reports of ADRs with *look-alikes* were excluded.
[2]PPA content (mg) of product is noted only when specified by author.

*indicates unspecified information.

ppalitne.tab

Table 8. Annual incidence of hemorrhagic stroke per 100,000 population[1] according to age at diagnosis, diagnostic type and community.

| Community | Year | Age (years) | Sex M/F | Total hemorrhagic | SAH[2] | ICH[3] |
|---|---|---|---|---|---|---|
| Rochester, Minn.[31] | 1945-54 | 15-29 | F | 0 | 0 | 0 |
| | | 30-39 | | 4.1 | 0 | 4.1 |
| | | 40-49 | | 23.0 | 9.2 | 13.8 |
| | | 15-49 | | 6.6 | 2.2 | 4.4 |
| | 1955-1966 | 15-29 | | 4.5 | 3.0 | 1.5 |
| | | 30-39 | | 6.2 | 3.1 | 3.1 |
| | | 40-49 | | 38.0 | 34.5 | 3.5 |
| | | 15-49 | | 12.4 | 10.1 | 2.3 |
| Goteborg, Sweden[32] | 1970-75 | 15-44 | F | 7.4 | 5.9 | 1.5 |
| | | 45-54 | | 47.2 | 30.1 | 17.1 |
| | | 15-54 | | 17.4 | 12.0 | 5.4 |
| Stockholm Co., Sweden[33] | 1973-1977 | 0-24 | F | 4.3 | 2.5 | 1.7 |
| | | 25-34 | | 9.4 | 7.3 | 2.1 |
| | | 35-44 | | 22.7 | 17.3 | 5.4 |
| | | 45-54 | | 46.4 | 27.9 | 18.5 |
| | | 0-54 | | 15.4 | 10.2 | 5.2 |
| United States (National Survey of Stroke)[34] | 1975-1976 | 0-44 | M/F | 2.8 | 2.1 | 0.7 |
| | | 45-54 | | 40.4 | 23.4 | 17.0 |
| | | 0-54 | | 8.0 | 5.0 | 3.0 |
| Florence, Italy[35] | 1983-1985 | 15-34 | M/F[4] | 3.1 | 1.7 | 1.4 |
| | | 35-44 | | 8.8 | 6.1 | 2.7 |
| | | 15-44 | | 5.1 | 3.2 | 1.9 |
| Lund-Orup, Sweden[36] | 1983-1985 | 15-54 | M/F | 7.4 | 3.6 | 3.8 |

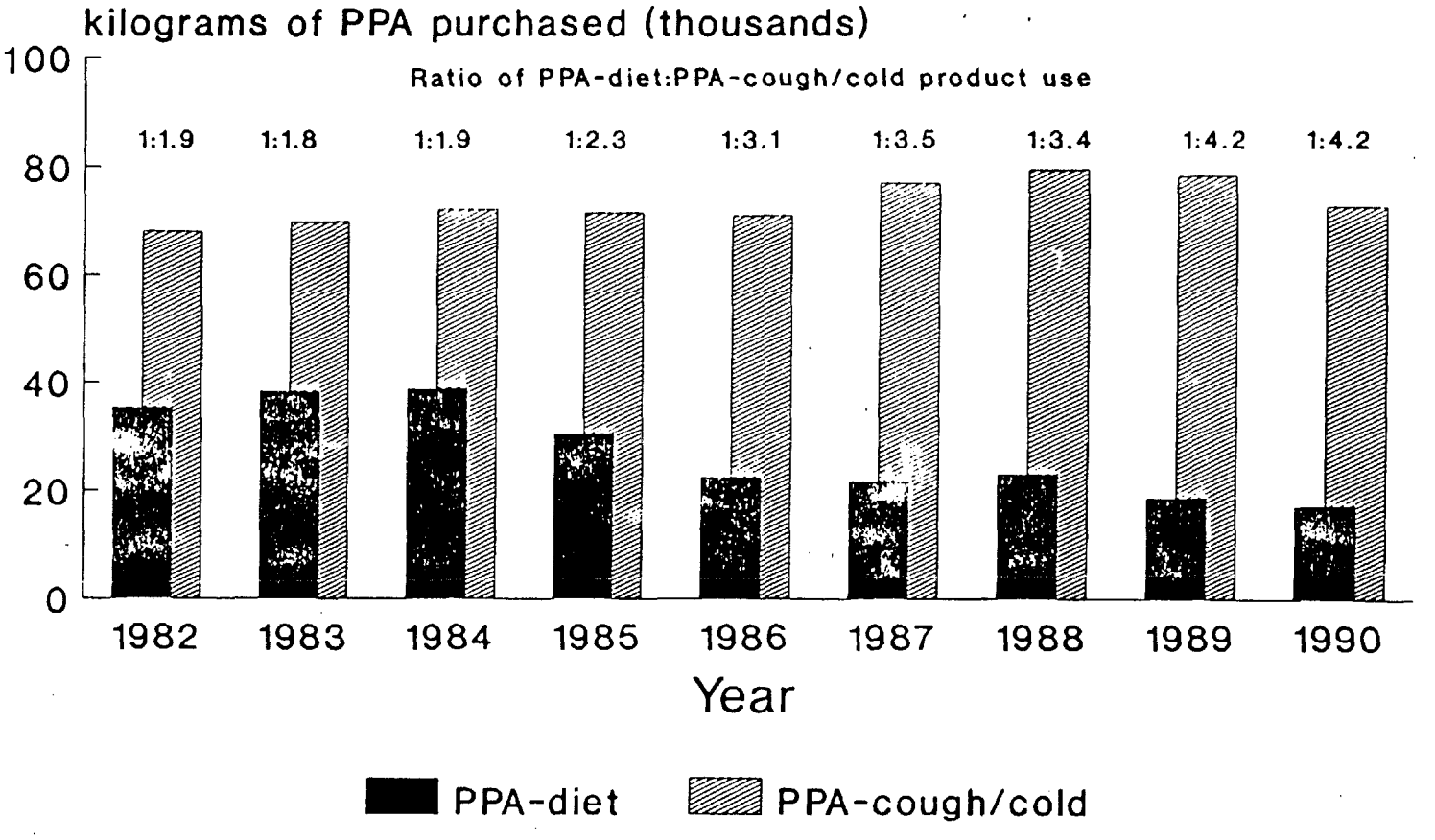
[1]Sex-specific incidence for women is given when published data were stratified by sex.

[2]SAH denotes subarachnoid hemorrhage.

[3]ICH denotes intracerebral hemorrhage.

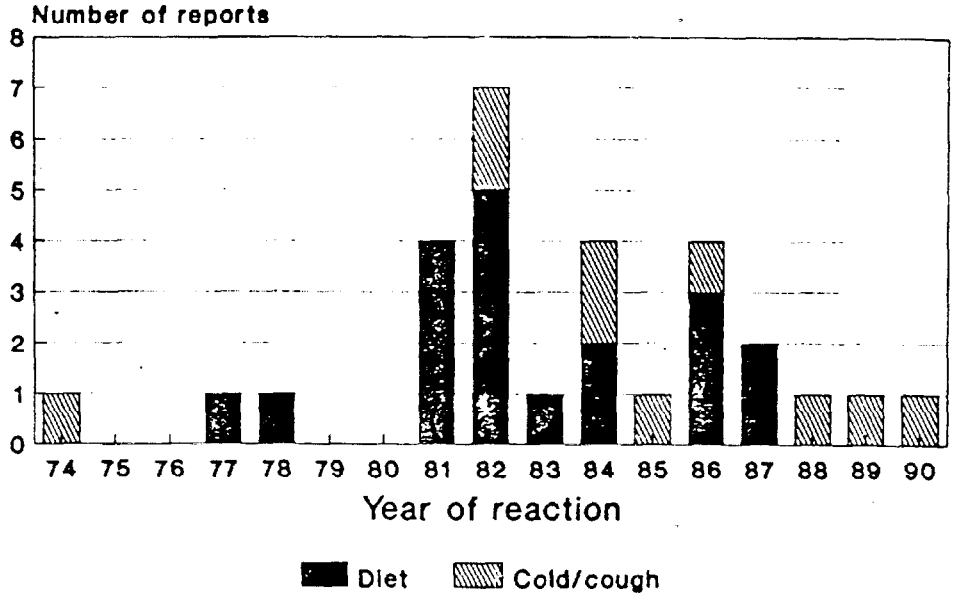
[4]Authors noted no difference in the frequency of types of stroke by sex except for a non-significant higher frequency of ICH in men.

# Purchases of Phenylpropanolamine by Type of PPA-product, 1982-1990



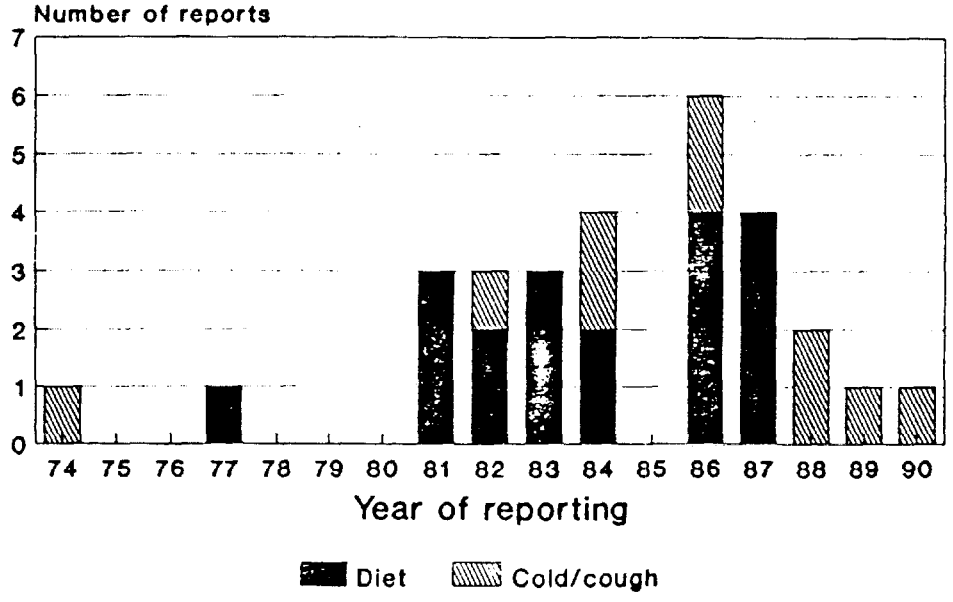

Source: U.S. Pharmaceutical Market-
Drug Stores and Hospitals,
IMS America, Ltd. Plymouth Meeting, PA.

## Reports of CVA Associated with PPA By Product and Year of Reaction




# Figures 2a and 2b

## Reports of CVA Associated with PPA by Product and Year of Report




source: Spontaneous Reporting System,FDA

## References:

1. Winick C. A comparison of the relative safety of phenylpropanolamine, acetaminophen, ibuprofen and aspirin as measured by three compendia. Int J Clin Pharmacol Ther Toxicol 1989; 27(6):267-272.

2. Raford P. Phenylpropanolamine diet pills: epidemiological surveys, adverse drug reactions, and contacts with poison control centers; a comparison with over-the-counter aspirin and acetaminophen. Testimony before the House subcommittee on Regulation, Business Opportunities, and Energy. September 24, 1990.

3.Letter from Joseph C. Veltri, Pharm.D., Director, Intermountain Regional Poison Control Center to Tim Dring, MS, CIBA Consumer Pharmaceuticals, October 4, 1990.

4.Wesson DR, Camber S. Phenylpropanolamine mentions in the Drug Abuse Warning Network: numbers plus interaction. in Phenylpropanolamine Risks, Benefits, and Controversies. Edited by JP Morgan, DV Kagan, and JS Brody. 1985. Praeger Publishers, New York.

5.Rosner BA. Fundamentals of biostatistics. Boston: Duxbury Press, 1982.

6.Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22:719-48.

7.Critique by Charles Winick, PhD on the Second Testimony by Paul Raford, M.D. Submission from Thompson Medical Company, Inc. to the FDA, January 1991.

8.Winick C. Assessing epidemiological relationships between strokes and phenylpropanolamine use. in Phenylpropanolamine Risks, Benefits, and Controversies. Edited by JP Morgan, DV Kagan, and JS Brody. 1985. Praeger Publishers, New York.

9.National Disease and Therapeutic Index. IMS America, Ltd. Plymouth Meeting, PA.

10.21 CFR 314.80 Postmarketing reporting of adverse drug experiences.

11.Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. Adv Inflam Res 1984;6:1-7.

12.McDowell JR, LeBlanc HJ. Phenylpropanolamine and cerebral hemorrhage. West J med 1985; 142:688-691.

13.Kirka DK, Devereaux MW, Chandar K. Intracranial hemorrhages due to phenylpropanolamine. Stroke 1985; 16(3):510-512.

14. O'Neill, RT, Van de Carr SW. A case-control study of adrenergic decongestants and hemorrhagic CVA using a Medicaid data base. (unpublished).

15.Jick H, Aselton P, Hunter JR. Phenylpropanolamine and cerebral hemorrhage. Lancet 1984; 1:1017 (letter).

16.Aselton P and Jick H. Phenylpropanolamine exposure and subsequent hospitalization. JAMA 1985; 253:977 (letter).

17.Rogers AS, Israel E, Smith CR, et al. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. Arch Intern Med 1988. 148:1596-1600.

18.Inman WHW, Vessey MP. Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. BMJ 1968; 2:193-199.

19.Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley and Sons, 1981.

20.Bernstein E, Diskand BM. Phenylpropanolamine: a potentially hazardous drug. Ann Emerg Med 1982; 11:311-315.

21.Johnson DA, Etter HS, Reeves DM. Stroke and phenylpropanolamine use. Lance 1983; 3:970.

22.Mesnard B, Ginn, DR. Excessive phenylpropanolamine ingestion followed by subarachnoid hemorrhage. South Med J 1984; 77:939.

23.Kizer KW. Intracranial hemorrhage associated with overdose of decongestant containing phenylpropanolamine. Am J Emerg Med 1984; 2:180-1.

24.Fallis RJ, Fisher M. Cerebral vasculitis and hemorrhage associated with phenylpropanolamine. Neurology 1985; 35:405-407.

25.Edwards M, Russo L, Harwood-Nuss A. Cerebral infarction with a single oral dose of phenylpropanolamine. Am J Emerg Med. 1987; 5:163-164.

26.Glick R, Hoying J, Cerullo L, Perlman S. Phenylpropanolamine: an over-the-counter drug causing central nervous system vasculitis and intracerebral hemorrhage. Neurosurgery 1987; 20:969-974.

27.Maertens P, Lum G, Williams JP, White J. Intracranial hemorrhage and cerebral angiopathic changes in a suicidal phenylpropanolamine poisoning. South Med J 1987; 80(12):1584-1586.

28.Kase CS, Foster TE, Reed JE, Spatz EL, Girgis GN. Intracranial hemorrhage and phenylpropanolamine. Neurology 1987; 37:399-404.

29.Maher LM. Postpartum intracranial hemorrhage and phenylpropanolamine use. Neurology 1987; 37:1686.

30.Forman HP, Levin S, Stewart B, Patel M, Feinstein S. Cerebral vasculitis and hemorrhage in an adolescent taking diet pills containing phenylpropanolamine: case report and review of literature. Pediatrics 1989; 83:737-741.

31.Schoenberg BS, Whisnant JP, Taylor WF, Kempers RD. Strokes in women of childbearing age. Neurology 1970; 20:181-189.

32.Harmsen P, Berglund G, Larsson O, Tibblin G, Wilhelmsen L. Stroke registration in Gotegorg, Sweden, 1970-75. Act med Scand 1979; 206:337-344.

33.Mettinger KL, Soderstrom CE, Allander E. Epidemiology of acute cerebrovascular disease before the age of 55 in the Stockholm County 1973-77: incidence and mortality rates. Stroke 1984; 15(5):797-800.

34.Robbins M, Baum HM. Incidence. Stroke 1981; 12, suppl 1:I-45-I-55.

35.Nencini P, Inzitari D, Baruffi MC, et al. Incidence of stroke in young adults in Florence, Italy. Stroke 1988; 19:977-981.

36.Norrving B., Lowenhielm P. Epidemiology of stroke in Lung-Orup, Sweden, 1983-85. Acta Neurol Scand 1988; 78:408-413.