Appendix D

Consumer Healthcare Products Association

Appendix D

Epidemiologic Analysis of the Purported Association of Phenylpropanolamine in Hydrochloride Diet Aids with Hemorrhagic Stroke in the 15-44 Year Old U.S. Female Population

September 3, 1991

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EPIDEMIOLOGIC ANALYSIS OF THE PURPORTED ASSOCIATION OF PHENYLPROPANOLAMINE HYDROCHLORIDE DIET AIDS WITH HEMORRHAGIC STROKE IN THE 15-44 YEAR OLD U.S. FEMALE POPULATION

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I. Introduction

A. Background

In the Federal Register of April 1, 1991 (56 FR 13295-99)[1], the Food and Drug Administration (FDA) announced the reopening of the administrative record (Docket No. 81N-0022) for Over-The-Counter (OTC) Weight Control Drug Products, and held a public feedback meeting on May 9, 1991, to consider new data relating to the safety and effectiveness of phenylpropanolamine hydrochloride (PPA) as an OTC appetite suppressant. On pages 13296-7 of the Notice, the Agency discussed their safety concerns relating to published (medical literature) and unpublished (FDA Spontaneous Reporting System, or SRS) reports of stroke and intracranial hemorrhage associated with use of PPA. The FDA postulated that a plausible representation of the effect of PPA might be case reports where there was a first dose/first day of use effect, perhaps in a hyperresponsive patient population. The Agency pointed out, however, that there have been few cases clearly fitting this description and, in fact, a hyperresponsive subpopulation has never been identified.

Additionally, the Agency mentioned that most of the medically serious reports involved single doses of at least 150 mg of PPA (or at least twice the recommended maximum daily appetite suppression dose of 75 mg), speculating that this "could suggest a dose response relationship".

The FDA said that "[a]ffecting all of the safety considerations is the extreme difficulty of evaluating isolated reports, often missing critical data, of relatively rare events, especially in the OTC drug-use setting, where use information is extremely sparse and little is known about reporting practices. These are problems with evaluation of any spontaneous reports, but evaluation is even more difficult in the OTC drug-use setting. Without knowledge of use patterns and the ages of users, the agency has found it very difficult to determine whether the reported instances of central nervous system bleeding are excessive in relation to background rate." The agency also

stated that very few reports existed of hemorrhagic stroke associated with PPA cough/cold product use.

On page 13298 of the Notice, the FDA posed the following question relating to the general safety of PPA appetite suppressants: "...do data suggest a real, even if small, ability of phenylpropanolamine hydrochloride to induce major central nervous system adverse events at the recommended dose or at slightly excessive doses, or are the reports of such events not distinguishable from the spontaneous rate of these events?"

B. Approach

This report provides an analysis of published and unpublished reports of hemorrhagic stroke purportedly associated with PPA diet aid use. These reports are analyzed in as complete a manner as possible given the limitations of available case report information. Reports involving PPA-containing diet aid products as well as PPA-containing cough/cold products are discussed because any analysis of a potential causal relationship must take into account the basic pharmacologic mode of action of a drug (in this case, PPA). For safety evaluation purposes, it is immaterial what the indication for use of a drug is if the strength, dosage form, route of administration, and population of users are comparable.

An assessment of the risk of hemorrhagic stroke associated with PPA diet aid use is presented in two stages: first, an estimate of the background rate of hemorrhagic strokes in the U.S. population was derived to give expected numbers of strokes; second, the observed (reported) number of strokes in the PPA diet aid user population was compared to the expected number of strokes in a manner analogous to a morbidity ratio. This was done by dividing the number of observed reports of hemorrhagic stroke purportedly associated with PPA diet aid use by the expected (background) number of hemorrhagic strokes in the U.S. female 15-44 year old PPA diet aid user population. In assessing risk, emphasis has been placed on the 15 to 44 year old U.S. female population since that subpopulation represents a large proportion of PPA diet aid users and it conveniently overlaps the age categories in databases from which background hemorrhagic strokes estimates are available. The calculated morbidity ratios presented herein, however, cannot be taken as absolute indicators of

risk because the components, namely: complete and accurate hemorrhagic stroke case report databases, complete knowledge of the size of the exposed population (i.e., the female diet aid user population) and accurate, stable background rates of hemorrhagic stroke in this same population are not available. Yet, these types of database deficiencies exist for most other drugs, prescription as well as non-prescription, making risk assessments difficult.

Finally, an analysis is provided of the degree to which the criteria for a possible causal relationship are satisfied for hemorrhagic stroke associated with PPA diet aid use.

Morbidity ratio calculations were performed utilizing observed numbers of hemorrhagic strokes purportedly associated with PPA single ingredient diet aids only, since PPA/caffeine combination ingredient diet aids have not been manufactured since the end of 1983 and are, therefore, not representative of the product for which monograph status is being determined.

C. Demographics and Product Use Patterns of the PPA Single Ingredient Diet Aid Consumer Population

Over the period 1983 to 1991, several industry-sponsored market research studies have been conducted to characterize the PPA diet aid consumer population.[2] Overall, 60% of this population consists of female consumers 15 to 54 years of age. Table 1 provides a more detailed estimate of the female 15-44 year old PPA single ingredient diet aid user population by five year increments in age for the years 1982, 1984, and 1989. This was estimated by applying the relative percent shelf offtake volume for PPA single ingredient diet aids to the overall percent of diet aid purchasers among the 15-44 year old U.S. female population as determined by market surveys completed in 1982, 1984, and 1989. An average user population for those three years was then calculated (arithmetic mean) to represent the user population over the period of this study (1980 through 1990). Again, the female 15-44 year old subpopulation has been selected for analysis since it represents a large proportion of the entire female PPA diet aid consumer population.

Market research has also provided information pertaining to product use patterns for both diet aid and cough/cold products. In heavy users who account for 80% of product usage, PPA diet aid use is typically seasonal in nature, with an average of two periods of use per year. These periods usually occur during March to June.[3] The number of consecutive days of product use is, on average,

16.5 days for an annual total of approximately 33 days. Product use typically occurs in conjunction with a reduced calorie diet and exercise. This regimen of use is reinforced and encouraged in the product labeling of the leading PPA diet aid brands. Some dieters, however, will also use the product sporadically, over the course of a year, for one to a few days at a time. This is particularly true if the consumer is attempting to limit their food intake for short periods of time (e.g., over holiday periods).

In comparing the exposure to PPA in all product forms, it is important to point out the differences and similarities between the consumer population of PPA diet aids and the consumer population of PPA cough/cold products. While diet aids are used predominantly by adult females, cough/cold products are used by all age groups of both genders, including pediatric use. While diet aid use is typically biannual for up to weeks at a time, cough/cold product use may be episodically more frequent with shorter periods of consecutive dosing (days rather than weeks) over the course of a year.[4] The average adult experiences two to three colds per year.[4] Peak usage can, and usually does, coincide with the Fall/Winter and Spring cold/flu seasons, as well as the Spring/Summer allergy season, thereby approximating the above-noted diet aid use periods.

D. Summary of Findings

Utilizing very conservative (i.e., worst case) analytical assumptions, the results of this epidemiologic analysis do not suggest or even signal a trend towards an increase in the risk of hemorrhagic stroke associated with PPA single ingredient diet aid use in the 15-44 year old U.S. female population.

Additionally, after considering the degree to which published and unpublished reports of hemorrhagic stroke associated with all forms of PPA use satisfy or do not satisfy the criteria for causal relationships, it is clear that such a possible relationship cannot be concluded on the basis of the available data.

II. Derivation of Number of Observed Reports of Hemorrhagic Stroke Purportedly Associated with PPA Diet Aid Use

A. Published and Unpublished Hemorrhagic Stroke Product Experience Reports Purportedly Associated with PPA Drug Products

Three sources of case report information were accessed in order to compile, sort, and tabulate product experience reports (PERs) of hemorrhagic stroke purportedly associated with PPA diet aid use: the medical literature, the FDA's Spontaneous Reporting System (SRS), and diet aid manufacturer PER files. For hemorrhagic stroke PERs purportedly involving PPA cough/cold products, only the SRS and medical literature databases could be accessed. PER files of manufacturers of PPA cough/cold products could not be accessed due to the proprietary nature of such information. Therefore, the total number of hemorrhagic stroke PERs purportedly associated with PPA cough/cold product use cited herein may be lower than the actual total due to unavailable manufacturer database PERs.

A total of 17 PERS (all ages and sexes) involving a hemorrhagic stroke purported to be in association with PPA diet aid or cough/cold product use over the period January 1, 1980 to February 28, 1991 have been published in the medical literature (includes one report that was published as well as filed to the SRS); 50 PERs (all ages and sexes) have been filed to the FDA's SRS database (two duplicate reports excluded; four additional reports involved PPA illegal combination products); and 10 PERs have been filed to PPA diet aid manufacturer PER databases. Of this total of 81 reports, 44 (54%) were associated with PPA diet aids, and 34 (42%) were associated with PPA cough/cold products. Since PER files of PPA cough/cold product manufacturers could not be accessed, the total number of hemorrhagic stroke PERs purportedly associated with PPA cough/cold products could not be compiled or verified, and may very well be higher than that stated above. On the basis of prior discussions with the FDA[5], the time period 1980 through 1990 was selected for tabulation/analysis purposes since it covers the period of peak marketing and affective product experience reporting. Table 2 lists total numbers of published and unpublished hemorrhagic stroke PERs for this time period for PPA diet aids, cough/cold products, and illegal combination products. Figure 1 illustrates the total number of published and unpublished PERs, by sex (all ages) and by year, of hemorrhagic stroke purportedly associated with PPA diet aid use over the period 1/80-12/90. Figure 2 illustrates in the same manner the total number of hemorrhagic stroke PERs for PPA cough/cold products over the same period less any unpublished PERs filed only to manufacturer databases. An overall comparison between PPA diet aid and cough/cold products of total purported hemorrhagic stroke PERs over time is illustrated in Figure 3. For detailed information on hemorrhagic stroke PERs, see Appendix A (PPA diet aid PERs) and Appendix B (PPA

cough/cold product PERs) in the report entitled "Integrated Summary of Hemorrhagic Cerebrovascular Events" for subject listings, FDA Forms 1639, and published case reports.

B. Published and Unpublished Hemorrhagic Stroke Product Experience Reports Purportedly Associated with PPA/Caffeine Combination Diet Aids.

Most of the hemorrhagic stroke PERs purportedly associated with PPA diet aid use involved PPA/caffeine combination diet aid products. Over the period 1/80 through 2/91, of the total of 44 PERs allegedly associated with PPA diet aids, 30 reports (68%) involved PPA/caffeine combination diet aid products. Of these 30 PERs, 6 reports involved ingestions of 3-12 times the maximum recommended dose, 3 reports involved contraindicated concomitant use of blood pressure medications or a history of hypertension, and 3 reports involved patients with arteriovenous malformations (AVMs) or a history of hydrocephalus. PPA/caffeine combination diet aid products usually contained 75 mg of PPA plus 200 mg of caffeine.

Approximately two-thirds of the reports purportedly involving PPA/caffeine combination diet aid products concerned ingested doses 2-12 times the maximum recommended dose (i.e., in excess of 200 mg caffeine; typical overdose case involved more than 400 mg caffeine). The daily intake of caffeine for the average American is approximately 200 mg/day, with 20-30% of the U.S. population consuming more than 500 mg/day from all sources. Most of the hemorrhagic stroke cases purportedly associated with PPA/caffeine combination diet aid use, therefore, are likely to have involved total doses of caffeine from the diet aid in excess of 400 mg in addition to the diet aid user's normal caffeine intake. PPA-caffeine combination diet aids have not been manufactured since the end of 1983 and have been phased out of distribution (per 48 FR 52513 of November 18, 1983). They are, therefore, not the PPA diet aid product for which Final Monograph status is sought. Since hemorrhagic stroke PERs involving PPA/caffeine combination diet aids are not relevant to an analysis of a current public health risk they are not included in the morbidity ratio calculations to assess such a risk.

C. Published and Unpublished Hemorrhagic Stroke Product Experience Reports Purportedly Associated with PPA Single Ingredient Diet Aids

Over the period 1/80 through 2/91, a total of 13 published and unpublished PERs purportedly associated with PPA single ingredient diet aid use (duplicate reports excluded) have been filed. For most of these PERs, the primary source of information was the FDA Form 1639 from which there was incomplete information regarding dose taken (amount and product description), time between dosing and onset of symptoms, diagnosis, concomitant medications, medical history, and outcome. Important information regarding other factors or behavior which could potentiate a hemorrhagic stroke such as cigarette smoking, alcohol use, oral contraceptive use, cocaine/amphetamine abuse, or unusual physical exertion was also not provided. Moreover, none of these reports could be independently verified by review of medical source documentation.

Based on previous discussions with the FDA[6], the population of greatest interest in regards to PERs of hemorrhagic stroke purportedly associated with PPA single ingredient diet aid use is the subpopulation of females 15-44 years of age since they represent a large proportion of female consumers (as well as all consumers) of diet aid products. Over the period 1/80 through 2/91, there have been a total of 8 reports involving females 15-44 years of age. Table 3 provides a breakdown of these reports, indicating numbers of cases involving overdose and/or contraindicated concomitant medications or conditions. Table 4 tabulates hemorrhagic stroke PERs by five year increments in age over the period 1/80-12/90 by year of event, indicating numbers of cases involving overdose and/or contraindicated medications or conditions of use. Over this period, the maximum reporting occurred in 1986 and 1987. No reports of any such purported association of hemorrhagic strokes with PPA single ingredient diet aid use have been filed since 1988.

Among the eight reports of hemorrhagic stroke purportedly associated with PPA single ingredient diet aid use involving females 15-44 years of age, two reports involved overdoses of PPA, usually intentional, possibly for the purposes of suicide. For the purposes of this analysis, overdose is defined as a dose exceeding 150 mg of PPA, or more than 2 times the maximum dosage (75 mg) specified in the product labeling or in the FDA's OTC Weight Control Drug Product monograph. These cases involved females 15-24 years of age.

As with concomitant MAOI use, PPA diet aid product labeling has specifically cautioned against use of the product by persons who suffer from high blood pressure. Among females

15-44 years of age, over the time period 1/80 through 2/91 there has been one hemorrhagic stroke PER involving concomitant use of a blood pressure-lowering medication (thus the patient could be assumed to have known that she was hypertensive). This report concerned a female 39 years of age.

Certain types of substance abuse, especially cocaine and alcohol use, are known risk factors for hemorrhagic stroke[7-10]. Over the period of study there was one hemorrhagic stroke PER associated with PPA diet aid use that also involved a patient identified as an illicit drug and/or alcohol user. This patient was a female 22 years of age. It is quite possible, given the period of study (early to mid 1980s) and the probable use of illicit drugs and/or alcohol by at least a portion of the female PPA diet aid user population, that additional cases involving concurrent illicit drug and/or alcohol use may have occurred among the total number of hemorrhagic stroke PERs not otherwise identified as involving such use. These cases would not likely be so identified because a hemorrhagic stroke patient or their family members (if they were aware of drug abuse by a family member) would not be likely to admit to illicit drug use when interviewed for case history purposes because of the potential for embarrassment or fear of criminal investigation/prosecution.

In one published report[11] of a series of seventy-five 15-55 year old patients who suffered aneurysmal cerebral hemorrhage not associated with PPA drug product use, 25% of the cases involved a hemorrhage preceded within 24 hours by significant consumption of alcohol. This publication reported further that, within the age group 15-40 years, alcohol-related cerebral hemorrhages comprise 33% of all cases. Thus, since actual illicit drug and/or alcohol use cannot be known for most of the eight hemorrhagic stroke PERs associated with PPA single ingredient diet aids, and since illicit drug and/or alcohol-related hemorrhagic stroke may represent an important factor in 15-44 year old females, the analysis reported herein is a very conservative one that does not assume or assess illicit drug and/or alcohol involvement when it was not mentioned in the PER case records.

D. <u>Underreporting of Hemorrhagic Stroke Product Experience Reports Purportedly Associated with PPA Diet Aid Use</u>

There are no good estimates of the extent of OTC drug product experience underreporting, although for prescription drugs it has been estimated that only 1 in 10 experiences are filed to the FDA's SRS database[12]. There is no basis in experience or medical literature to conclude that

underreporting of hemorrhagic strokes associated with PPA drug product use might be as bad as, or any worse than 1 in 10 for the following reasons:

1.) The magnitude of PER underreporting relates to three factors: the correct diagnosis of a hemorrhagic stroke event, the identification of the temporal association of PPA diet aid use with the event, and the reporting of the event to one or more of the three PER databases (FDA, literature, company files). Significant underreporting is doubtful because hemorrhagic stroke is a serious event almost certainly resulting in hospitalization, physician intervention, and rigorous evaluation, especially if the stroke has occurred in a young woman. Thus, misdiagnosis of the hemorrhagic stroke is unlikely. The evaluation would include a thorough history of medication use, both prescription and OTC. Further to the point, PPA's alleged association with hemorrhagic stroke has been the subject of significant controversy for several years, especially in the medical literature but also to a significant extent in the lay press. Thus misidentification of a temporal association, as well as non-reporting of the event is unlikely.

2.) Besides the possibility of PER underreporting, there is also the possibility of PER overreporting.[13] In 1983 and 1984, Congressional hearings held by Rep. Mary Rose Okar questioned the safety of PPA, resulting in a barrage of related literature reports as well as heightened media attention. It also provoked the Center for Science in the Public Interest (CSPI) to issue a call for hemorrhagic stroke experience reports in 1984, a point in time which coincides with the period of maximum reporting discussed above. It is likely, therefore, that the rate of reporting of purported hemorrhagic stroke PERs associated with PPA diet aids could have been influenced by a type of bias resulting from media publicity that would encourage reporting of <u>any</u> PER associated with PPA diet aids, even when its occurrence was doubtful. Media bias has been reported to have occurred for other drugs besides PPA.[14]

In comparing the observed number of hemorrhagic stroke PERs to the expected number of hemorrhagic stroke cases for the PPA diet aid user population of 15-44 year old females, it

was observed that annual numbers of hemorrhagic stroke PERs by five year age group were highly variable, with no reported cases for some five year age groups in most years. Therefore, morbidity ratio calculations were performed to cover the entire eleven year period of study (1980 through 1990) for all female age groups within 15-44 years combined in order to take into account the instability of annual reporting rates. For one analysis a PER underreporting factor of 1 in 10 was applied to the overall number of PERs for the 15-44 year old category, rather than in an individual 5 year age group, since it cannot be assumed that this factor applies equally across all age groups.

III. Derivation of Background Number of Hemorrhagic Strokes Expected in the U.S. Female 15-44 Year Old Diet Aid User Population

In order to calculate a morbidity ratio and thereby estimate the risk associated with use of PPA diet aids, it was necessary to obtain the expected number of hemorrhagic strokes in the female diet aid user population, assuming all factors apply. To this end, it was desirable to utilize a stroke surveillance database that is best representative of the U.S. population in terms of race, ethnicity, socio-economic status, medical knowledge, quality of medical care, and access to medical care. This database should also be appropriately large enough to yield a sufficient number of stroke cases to allow suitable analysis. For this purpose, the National Hospital Discharge Survey of the National Center for Health Statistics was selected.

A. National Hospital Discharge Survey-Derived Rates

The National Hospital Discharge Survey (NHDS)[15], conducted and reported by the National Center for Health Statistics, comprises unbiased statistical estimates of diagnoses, days of care, and medical procedures utilized for patients discharged from non-institutional hospitals (exclusive of military, Federal, and Veterans Administration hospitals) located in the fifty States as well as the District of Columbia. To be included, a participating hospital must have at least six beds and admit patients for stays of less than thirty days in length (i.e., short stay hospitals versus chronic care facilities). NHDS-reported estimates of diagnoses/days of care/procedures are derived by stratified sampling of discharge records from a subset of the total number of qualifying hospitals. As an example, in 1986 a total of 193,000 abstracts of medical records were obtained from 418 participating hospitals (from a total random sample that year of 558 hospitals). Diagnoses and medical procedures are coded in the Survey according to the International Classification of Diseases[16].

Diagnoses are further delineated as first-listed (i.e., primary) and all-listed diagnoses up to a maximum of seven diagnoses per patient. For the purposes of this report, the ICD Code numbers of interest are 430 (subarachnoid hemorrhage), 431 (intracerebral hemorrhage), and 432 (other and unspecified intracranial hemorrhage).

As with any survey, the estimates are subject to various types of errors such as non-sampling (measurement) error, sampling error, and errors in diagnoses (which is independent of the survey). Additionally, the NHDS sampling frame was redesigned in 1988 resulting in some variation in longitudinal trend data. The relative standard error for diagnosis estimates ranged from 12-14 percent for individual years over the time period of this report (1979 to 1988) (direct communication with the National Center for Health Statistics, 1991).

Specific to estimates of hemorrhagic stroke incidence is the possibility that such stroke diagnoses are not always the first-listed diagnosis. The NHDS also does not include diagnoses estimates for patients who died prior to hospital admission or who were not admitted to the hospital for other reasons. Thus, including only primary hemorrhagic stroke diagnoses may underrepresent the actual number that occurred. However, some overestimation may occur as well. First (i.e., initial) strokes are not distinguished in the database from recurrent strokes. It should be pointed out that improvements in diagnostic techniques and, therefore, the ability to correctly diagnose a particular type of stroke can also affect estimates of diagnosis from year to year and within certain ICD Code numbers (namely, Code Nos. 430, 431, and 432).

On the basis that estimates of diagnoses in the NHDS database are derived from a statistically valid sampling procedure of short-stay hospitals and their medical records, estimation of hemorrhagic stroke rates in the U.S. population from the NHDS is an appropriate technique. In fact, there is precedence in the medical literature for this approach in evaluating disease rates in general[17-30] and for hemorrhagic stroke rates in particular[31].

One advantage associated with use of the NHDS in estimating stroke rates is that, rather than being either a cross-sectional sample[32,33] or localized to a small geographic area (as most stroke registries are)[34-36], the NHDS provides longitudinal data and is statistically

representative of the U.S. short-stay hospital population. This is particularly important if, as has been reported in the literature[37], the overall incidence of hemorrhagic stroke in the U.S. population is changing over time. An additional advantage to the NHDS is the public availability of datatapes to allow age-sex specific tabulations of rates, a feature typically not available with stroke registries.

Average annual rates for ICD Code Nos. 430, 431, and 432 (shown as 430-432) were calculated for the 15-44 year old U.S. female population by 5 year age group from estimates of first-listed (primary) diagnoses of these ICD codes. The estimates were obtained directly from the NHDS datatapes for 1979, 1980, and 1982 through 1988 (1981 datatapes were not available). ICD Code No. 436 (acute, but ill-defined cerebrovascular disease) was not considered specific enough to hemorrhagic stroke [especially with the availability of computed tomography (CT) and angiographic diagnostic techniques over much of the nine-year period] and was therefore not included in the tabulation. The reason for the notable increase in the rate of ICD Code Nos. 430-432 for 40-44 year old U.S. females from 7.76/100,000 in 1982 to 36.51/100,000 in 1988 is not known.

Age-sex specific rates of ICD Code Nos. 430-432 for each year were calculated by dividing estimated diagnoses in each 5 year age category by the appropriate age-sex specific annual census population (U.S. Bureau of Census estimates). These rates were then averaged over the nine year period under study and expressed per 100,000 population. Table 5 provides annual and nine-year average rate estimates of hemorrhagic stroke in U.S. females 15-44 years of age. Expected numbers of hemorrhagic strokes in U.S. female single ingredient diet aid users 15-44 years of age over the eleven year study period are listed in Table 6 by five year increments in age. These estimates are tabulated assuming 33 multiple exposures/year, and two first-dose exposures/year. The background numbers of expected strokes were calculated by applying the nine-year average NHDS-derived rate to the exposure-adjusted female PPA single ingredient diet aid user population (1982-89 average user population from Table 1) . Estimates of expected strokes assuming various days (exposures) at risk were calculated (in response to a request by the FDA[38]) assuming a constant hazard function; i.e., that all factors associated with hemorrhagic stroke would apply with equal force on each day of the year. To be noted, however, is that factors associated with hemorrhagic stroke do not, in fact, apply with equal force every day of the year. This is

particularly true for factors that affect blood pressure, which can apply with varying degrees of force over the course of a day, a week, or a year.

B. Comparability of NHDS-Derived Annualized Rates to Those from Other Databases

A useful and reasonable comparison can be made by examining NHDS-derived hemorrhagic stroke rates and rates from other U.S. and foreign databases. For instance, the utility of an NHDS-derived rate as a measure of the "background" rate of hemorrhagic stroke can be assessed by comparison to hemorrhagic stroke rates in Canada, where over-the-counter (OTC) PPA-containing cough/cold products, but not diet aids, are available. Table 7 provides tabulations of the age-sex specific hemorrhagic stroke rates (ICD Code Nos. 430-432) for the U.S. and Canada, while Figures 4 through 7 are comparative plots of the same rates for each age category. The Canadian database includes all discharges for the entire Canadian population, rather than estimates based on sampling procedures (direct communication with Canadian Center for Health Statistics, 1991). For this reason the rates are more stable from year to year than the NHDS-derived rates. Other than the fact that the Canadian registry is not an estimate of diagnoses based upon a stratified sample, the same types of systematic diagnostic and mis-classification errors found in the NHDS apply to the Canadian database.

As can be seen in Table 7, the NHDS-derived rates are comparable to the Canadian rates over the same nine-year period (1979-1988). Given that the Canadian population is roughly comparable to the U.S. population in terms of general hemorrhagic stroke risk factors[35,39-41] and potential exposure to PPA-containing drug products (except, notably, the availability and use of PPA diet aids), the comparability of rates serves to put the NHDS-derived rates in perspective.

There is also evidence of comparability of the NHDS-derived rates to other stroke rates reported in the literature. Table 8 illustrates this by providing a comparison of rates for subarachnoid and intracerebral hemorrhage (ICD Code Nos. 430 and 431, respectively) in U.S.[42], Swedish[43], Italian[44], New Zealand[45], Finnish[46], and Icelandic[47] populations. The comparability of databases in terms of ICD Code No. 432 could not be assessed since this diagnostic code was not included in some of the published reports.

The stroke database compiled by the Mayo Clinic for Olmstead County (Rochester), MN was not utilized as a source of background stroke rates for numerous reasons. First, nearly 100% of the Olmstead County population is white and, principally, of Northwest European (e.g., German and Scandanavian) descent. Second, the majority of the adult population is employed by the two large health care establishments in the locality, providing for the population excellent preventive and remedial health care. Third, Olmstead County has a relatively small population base (approximately only 55,000). Finally, the Olmstead County database has historically produced small numbers of hemorrhagic stroke cases which, for a relatively rare disorder as stroke is for the younger adult population, does not allow for the computation of stable disease rates. The Olmstead County database is, therefore, not representative enough of the U.S. population at large and would be atypical of the PPA diet aid user population.

IV. Comparison of Number of Observed Reports of Hemorrhagic Stroke Purportedly Associated with PPA Single Ingredient Diet Aids to Expected Number of Hemorrhagic Strokes in U.S. Female 15-44 Year Old Diet Aid Population

A. Estimation of Morbidity Ratios

Morbidity ratios, under different sets of exposure/risk assumptions, have been estimated by comparing the observed number of hemorrhagic strokes associated with PPA single ingredient diet aid use to the expected number of hemorrhagic strokes associated with all factors for females 15-44 years of age. As discussed previously, these calculated ratios can be affected by imprecision in the observed and expected numbers of strokes due to limitations in the databases from which the numbers were derived. Tables 9-12 list eleven year average observed and expected strokes, in addition to a calculated morbidity ratio, for the following sets of assumptions:

Multiple-Dose Risk Assumption

Table 9: ratio of observed: expected strokes (all PERs included); assumes 33 days at risk per year (from two periods of use per year, with 16.5 days of consecutive dosing per period). There were 8 PERs which possibly were multiple dose cases.

Table 10: ratio of observed: expected strokes (excludes PERs involving overdose and/or contraindicated medications or conditions of use); assumes 33 days at risk per year as in Table 9. There were 4 PERs which possibly were multiple dose cases.

First-Dose Risk Assumption

Table 11: ratio of observed: expected strokes (all first day PERs included); assumes two days at risk per year. There were 5 PERs which possibly were first-dose cases.

Table 12: ratio of observed: expected strokes (excludes first day PERs involving overdose and/or contraindicated medications or conditions of use); assumes two days at risk per year. There were 2 PERs which possibly were first-dose cases.

Ratios are tabulated for the overall female 15-44 year old diet aid user population for the period 1/80 through 12/90. An underreporting factor of 1 in 10 is applied to the overall 15-44 age group total number of observed stroke cases, with a separate calculated ratio.

It is important to note that the assumptions and calculations for Tables 11 and 12 (first day risk) do not take into account other potential first dose exposures to PPA; i.e., first-dose exposures to PPA resulting from use of PPA cough/cold products during the year for treatment of cold and/or flu symptoms and/or symptoms of allergic rhinitis. Market survey data indicate that exposure could be up to 3 first-dose episodes per year. The PPA cough/cold user population is much larger (approximately 3 times larger) than the PPA diet aid user population, and it is reasonable to assume that a PPA diet aid user would be just as likely to use a PPA cough/cold product as a non-dieter; therefore, exposure to PPA among female dieters would likely involve both diet aid as well as cough/cold products. Potentiation of a hemorrhagic stroke would be a basic pharmacologic effect that could occur in the same manner no matter what indication for which the dosage form was labelled.

B. Observations/Discussion

The objective of this analysis was to compare the number of observed cases (PERs) of hemorrhagic stroke associated with PPA single ingredient diet aid use by females 15-44 years of

age to the spontaneous rate of hemorrhagic stroke events in the same population. The method of comparison selected was a morbidity ratio with the expected number of hemorrhagic stroke cases estimated from the NHDS. This approach could serve to answer the question of whether or not the number of observed cases is in excess of the background occurrence of hemorrhagic stroke. Again, it is important to point out that these calculated ratios are not absolute indicators of risk due to limitations in the data from which observed/expected numbers of hemorrhagic strokes were derived. A morbidity ratio of 1.0 could mean that a 15-44 year old female PPA diet aid user could be equally likely to develop a hemorrhagic stroke whether or not she is exposed to PPA diet aids. A ratio greater than 1.0 could mean that a person is at greater risk of developing a hemorrhagic stroke from PPA diet aid use than from other risk factors. However, because of the effects that other factors independent of PPA diet aid use may have in potentiating hemorrhagic strokes, morbidity ratios in excess of 1.0 are not necessarily conclusive evidence of increased risk[48].

1. Multiple Dose Risk Assumption

Tables 9 and 10 provided calculations of morbidity ratios for female 15-44 year old PPA single ingredient diet aid users for the period 1980-1990 assuming a cumulative risk of stroke associated with multiple consecutive doses of PPA. Table 9 included all hemorrhagic stroke PERs, while Table 10 excluded those PERs involving overdose and/or contrainidicated medications or conditions of use.

From Table 9 (all PERs), the overall eleven year average ratio for female 15-44 year old PPA diet aid users was 0.03. When adjusted for 1 in 10 PER underreporting, the eleven year ratio was 0.33. By excluding PERs involving overdoses and/or contraindicated medications or conditions of use in Table 10, the eleven year ratio for 15-44 year old females drops to 0.02, with the adjusted ratio (for underreporting of 1 in 10) being 0.16.

The construction of these tables, in terms of expected cases of hemorrhagic stroke, assumed a cumulative risk of stroke associated with multiple consecutive doses of PPA. From market research, average PPA diet aid usage comprises two periods of use per year of 16.5 days per period, for a total number of 33 consecutive dosing days per year. Expected numbers of stroke cases were

then calculated for 33 days of risk per year. On this basis, it can be seen from the resultant morbidity ratios that, on a multiple dose basis, there is no apparent increase in risk of hemorrhagic stroke associated with use of PPA diet aids.

2. First Dose Risk Assumption

Tables 11 and 12 provided calculations of morbidity ratios for female 15-44 year old PPA single ingredient diet aid users for the period 1980-1990 assuming risk of stroke on a first-dose/first day exposure basis, assuming 2 first dose exposures per year. Table 11 included all first day (assumed to be first dose) hemorrhagic stroke PERs, while Table 12 excluded all hemorrhagic stroke PERs involving overdose and/or contraindicated medications or conditions of use.

From Table 11 (all PERs), the overall eleven year average ratio for female 15-44 year old PPA diet aid users was 0.36. When adjusted for 1 in 10 PER underreporting, the eleven year average ratio is 3.57.

From Table 12, by excluding PERs involving overdose and/or contraindicated medications or conditions of use, the overall eleven year average ratio dropped from 0.36 (Table 11) to 0.14. The adjusted ratio (for 1 in 10 underreporting) was 1.43.

In performing the calculations of expected number of stroke cases in this manner, and comparing this number to the observed number of stroke cases, it can be seen from the resultant morbidity ratios that a meaningful increase in risk of hemorrhagic stroke associated with first-dose use of a PPA diet aid cannot, in general, be concluded. This is true for almost all the calculated ratios even if underreporting of 1 in 10 is assumed. The single exception was the calculated ratio for all reports (including overdose and/or contraindicated medications/conditions) under a first dose risk assumption (3.57 in Table 11). However, this ratio drops to 1.43 when PERs involving overdose (i.e., greater than twice the maximum total daily dose of 75mg PPA) and/or contraindicated medications/conditions are deleted. It is appropriate to exclude these cases since they represent improper use of the product beyond the labeled therapeutic dose. Also, the first dose risk calculation considered exposure only to PPA diet

aids. A more accurate assessment should include all possible forms of exposure to PPA to quantify the number of days at risk per year. As such, a 15-44 year old female dieter might be exposed to first dose effects on four occasions per year: two exposures related to two first day uses of PPA diet aids per year, and two to three exposures related to two or three first day uses of PPA cough/cold products per year (assuming two or three colds and/or allergy attacks per year). This type of assessment could not be done due to the unavailability of PPA cough/cold product hemorrhagic stroke PERs from manufacturer databases.

V. Considerations Regarding the Possible Relationship between PPA Diet Aid Use and Reports of Hemorrhagic Stroke in U.S. Females 15-44 Years of Age

The determination of whether a causal relationship exists between PPA diet aid use and reports of hemorrhagic stroke requires that the five criteria for a causal association be satisfied to at least some extent, namely: coherence of the events (i.e., biological plausibility), consistency of the events, timing of exposure to event, specificity of the reaction to the exposure, and the strength of the association of exposure to event[49]. While satisfaction of any one of the five criteria is insufficient to conclude that a causal association exists, satisfaction of all five criteria is not absolutely necessary for an association to be causal. The more criteria that are satisfied, the more likely it is that an association is causal. In the case of the association of PPA diet aid use with hemorrhagic stroke, it can be seen that none of the five criteria are satisfied sufficiently to permit a conclusion that a causal relationship exists.

A. Coherence of the Relationship (Biological Plausibility)

In the case of drug products, coherence of the events in the context of causal relationship means that there must be some pharmacologic mode of action, or drug effect, demonstrable in the animal (preferably human) model that could be linked to the effect being observed; in this instance, hemorrhagic stroke. For PPA, it has been suggested that its potential for elevating blood pressure and/or a speculated potential for causing vasculitis could be possible modes of action for causing hemorrhagic stroke[50]. If this were the case, it would be a mechanism of action associated with all forms of

exposure, diet aids as well as cough/cold products since both oral dosage forms contain PPA. However, careful review of available data does not lead to the conclusion that these postulated mechanisms are viable ones. Additionally, as discussed earlier, the elevations in blood pressure observed following normal doses of PPA are smaller than those induced by moderate physical activity or ordinary psychological stress, such as seeing a physician or taking an examination in school.

1. Blood Pressure Elevations Associated with PPA Use

Like all other sympathomimetic drugs, PPA can induce small to modest elevations in blood pressure. PPA's potential for elevating blood pressure has been well characterized in clinical trials. In 38 long and short term (i.e., single dose) clinical trials of over 3000 normotensive and mild, stable hypertensive subjects, it has been demonstrated that therapeutic doses of PPA do not cause clinically meaningful increases in blood pressure or significant side effects. In fact, the average 3-5 mm Hg increase that is observed is well within, if not significantly lower than, elevations observed in connection with normal activities such as bowel movements, moderate physical activity, or watching exciting television shows. A subpopulation of patients who may be hyper-responsive to the blood pressure elevating effects of PPA has not been identified in either clinical trials or post-marketing surveillance.

The elevation in blood pressure observed following a dose of PPA is transient in duration, and well within the range that the body's caroticoaortic baroreceptor defense mechanism is capable of adjusting. Repeat dosing of PPA produces gradually increasing tolerance to the point where product use of this kind produces little, if any, change in systolic or diastolic pressure over baseline.

On the basis of the extensive clinical and post-marketing database which demonstrates that PPA has minimal, if any, potential for causing significant elevations in blood pressure, it is difficult to postulate that this drug effect could be a key factor in the development of hemorrhagic strokes.

2. Potential for PPA-Induced Vasculitis

Vasculitis is a general term describing the inflammation of and damage to blood vessels. This syndrome has been observed following cerebrovascular hemorrhage[51-53].

Several publications have reported small-vessel vasculitis, beading, or segmental narrowing follow cerebral hemorrhages associated (temporally) with use of PPA[54-63]. On the basis of these observations, it was postulated that PPA could have been a causative agent in the development of a type of hypersensitivity vasculitis. In all of these reports, however, post-hemorrhage angiography had been utilized, and there was no possible way to determine the pre-hemorrhage condition of the cerebral vasculature. As such, and in combination with the knowledge that vasculitis has been commonly observed following cerebral hemorrhage independent of PPA use, it cannot be concluded that PPA is the causative agent in the development of small-vessel vasculitis. The angiographic evidence of vasculitis following a cerebrovascular hemorrhage associated with PPA is not, therefore, evidence of a mechanistic association, but rather a probable interpretation error of a usual outcome of hemorrhagic strokes.

In the absence of blood pressure elevation and/or drug-induced vasculitis, there is clearly a lack of any clinically demonstrable mechanism of drug action that could potentiate hemorrhagic strokes. In terms of a PPA-independent biological mechanism for hemorrhagic stroke, it is important to point out that AV malformations or sacular aneurisms are more likely to rupture during periods of greater physical activity (e.g., jogging). Under these circumstances, the systolic blood pressure increases while the diastolic pressure remains the same, increasing pulse pressure to the point where thin-walled blood vessels can rupture. The implication is that female dieters attempting to lose weight through a regimen which includes vigorous physical activity are already at risk of a hemorrhagic stroke, independent of PPA use, if they have an underlying condition of AV malformation or sacular aneurism.

B. Consistency of the Relationship

Consistency refers to the repeated observation of an association in different populations under different circumstances. Careful evaluation of the PPA diet aid-associated hemorrhagic stroke database reveals major inconsistencies in terms of dose taken, duration of therapy, time between dose and event, and other potentially confounding factors.

Five out of eight (62.5%) hemorrhagic stroke PERs associated with PPA single ingredient diet aids have involved (in some cases, suicidal) overdoses of PPA. Yet, the hemorrhagic stroke PER database apparently contains very few cases (two PERs possibly out of eight) involving patients suffering from eating disorders who typically misuse PPA diet aids in large quantity and have been reported to develop hemorrhagic strokes. It would seem, therefore, that ingestion of large quantities of PPA single ingredient diet aids is not consistently predictive of hemorrhagic stroke events. One out of eight PERs involved contraindicated concomitant medications or pre-diagnosed medical conditions (e.g., hypertension). It is important to reiterate that there have been no reports of hemorrhagic stroke associated with PPA single ingredient diet aids since 1988. There have been sixteen reports of hemorrhagic stroke purportedly associated with PPA cough/cold products since 1988, but this may simply be a factor of the broader and more frequent population exposure to PPA cough/cold products and/or other factors.

C. Timing of Exposure to Event

While it appears that, in hemorrhagic stroke reports for which case information is available, a dose of PPA preceded at some point in time the reported event, what is not clear is the amount of elapsed time between dose and event, and how that might relate to a pharmacologic effect or to the half-life (4.5 to 6.0 hours following oral administration) of the drug. What is even more confusing is that, while some reports appear to have involved a response to a first dose, other reports involved a response to multiple doses taken over an extended period of time. This variation in timing does not indicate any particular trend in the timing of the dose to event.

D. Specificity of the Reaction to the Exposure

The criterion of specificity implies the precision with which one component of an associated pair can be utilized to

predict the occurrence of the other; i.e., how frequently the presence of one variable (e.g., hemorrhagic stroke in young females) will predict in the same individual the presence of another (e.g., PPA diet aid use). Again, based on an analysis of case reports for which detailed information is available, it becomes readily apparent that there is wide variation in the circumstances associated with, as well as the etiology of, the hemorrhagic stroke event. This wide variation becomes particularly troubling if one is trying to deduce or define a potential mechanistic effect of PPA. Additionally, alternate causes of the disease event of concern, as well as confounders of the relationship examined should be systematically excluded. In this context, concomitant alcohol use, cigarette smoking, oral contraceptive use, cocaine/amphetamine use, head injury, migraine headache or unusual exertion are not systematically excluded; they are not even mentioned in most cases. Also, erroneous or incomplete patient recall of drug product use, particularly diet aid product misidentification (i.e., non-PPA products being identified as PPA-containing diet aids, a misidentification problem which has been observed in recent consumer surveys), can greatly affect the accuracy of hemorrhagic stroke case reports and, therefore, assessments of causality. In short, available case report information does not support the conclusion that PPA use would be predictive of a specific effect in terms of hemorrhagic stroke.

E. Strength of the Association of Exposure to Event

The strength of an association is not necessarily a biologically consistent feature, but rather a characteristic that depends on the relative prevalence of other causes. In this context, it is important to note the comparison (discussed previously) between the observed number of reports of hemorrhagic stroke associated with PPA diet aid use and the expected number of hemorrhagic strokes in the same population associated with all potential factors.

While the overall risk for young U.S. females of hemorrhagic stroke is low, it is not trivial. For example, the nine-year average NHDS-derived background rate of hemorrhagic stroke in U.S. females 15-44 years of age is 8.2 per 100,000 population per year; that is, one would expect to observe an approximate total of 237 hemorrhagic strokes per year among the female 15-44 year old PPA single ingredient diet aid user population assuming all possible risk factors apply. That there have been no published or unpublished reports of hemorrhagic stroke associated with

PPA diet aids since 1988, while a total of 474 (237/year x 2 years) strokes likely to be independent of exposure to PPA would have been expected (1989 through 1990), is a telling argument that the association of PPA exposure to hemorrhagic stroke events is weak.

VI. Conclusions

This report provides the results of a conservative (i.e., worst case) and rigorous analysis of published and unpublished reports of hemorrhagic stroke in young females associated with use of PPA single ingredient diet aids. These reports have been compared quantitatively to the background number of hemorrhagic strokes expected in the same female population resulting from all potential risk factors. These reports have been collectively evaluated to assess trends as well as to determine how well they satisfy the criteria for a causal relationship.

There are severe limitations to assessing or concluding causality from product experience reports. In many instances, important information is not available to accurately characterize the event. For example, recall bias, particularly in an emergency room setting, can confound the proper identification of drug doses or other factors that preceded the event. In this regard, recall of the elapsed time between dose and event is critical to assessing causality, yet the hemorrhagic stroke database for PPA is deficient in providing this key piece of information. The case reports also do not adequately describe the circumstances leading up to the event, namely: medical history, concomitant drug use, intake of alcohol or illicit drugs, etc. However, these types of PER database limitations exist for the majoirty of drug products, both prescription and non-prescription, making causality assessments difficult.

Examination of the hemorrhagic stroke database for PPA diet aids reveals a decline in the number of case reports over the eleven year period studied, and there have been no reports since 1988. While the overall rate of underreporting of product experience reports for OTC drug products (which can vary with the severity of the event as well as the accuracy of patient recall), is debatable, it certainly would not be expected for PPA-associated hemorrhagic strokes to exceed the historically-estimated rate of 1 in 10 because of the type of event being reported. As discussed earlier, hemorrhagic stroke in a young woman is a serious event resulting in hospitalization and physician intervention. Combined with the publicity PPA has had in the medical and lay press for close to ten years, it is difficult to believe that all three databases examined (FDA's SRS, medical literature, and company files) would miss 90% or more of these events if they were anything but extremely rare in occurrence.

Considering that a total of sixteen reports of hemorrhagic stroke have been filed since 1987 for PPA cough/cold products, one would expect at least one report since 1988 associated with PPA diet aids in at least one of the three databases. It must be emphasized that there have been no reports associated with PPA single ingredient diet aids since 1988.

When one quantitatively compares, in a manner analogous to a morbidity ratio, the observed reports of hemorrhagic stroke associated with PPA single ingredient diet aids to the expected number of hemorrhagic strokes in the same female diet aid user population, one generally finds that the risk associated with PPA single ingredient diet aid use is small compared to the risk associated with other factors independent of PPA use. In those specific instances in the analysis where the calculated ratio was in excess of 1.0 (suggesting increased risk), examination of the PERs contributing to that result reveals that, in most cases, the PERs involved (usually suicidal) overdoses and sometimes concomitant or illicit drug use as well. This analysis was the first-dose per year risk assumption which, as explained earlier, may be flawed since all forms of exposure to PPA are not considered. Cases involving overdose and/or concomitant/illicit drug use can confound any analysis of causality. Although this analysis included, as well as excluded, these PERs in calculating a morbidity ratio, a case can be made for their exclusion from consideration on the basis that these circumstances do not represent normal, therapeutic use of the drug product by the user population at large. It is clear, however, from the results of this analysis that the risk of hemorrhagic stroke associated with normal therapeutic doses of PPA for appetite suppression, if it exists at all, is low. Other risk factors such as illicit drug (especially cocaine), alcohol, oral contraceptive, and tobacco use as well as migraine headaches and low serum cholesterol can potentially contribute more to the development of a hemorrhagic stroke in young female dieters than use of PPA single ingredient diet aids.

It is difficult to conclude a mechanistic effect for PPA on the basis of a modest potential for elevating blood pressure since other types of everyday stimuli produce far larger transient elevations in blood pressure. The suggestion that a small hyperresponsive, idiosyncratic subset population may exist as an explanation for hemorrhagic stroke events associated with PPA use is flawed since there is no clinical evidence to support its existence. Observations of post-stroke vasculitis in conjunction with cerebrovascular hemorrhages associated with PPA diet aid use do not constitute conclusive evidence that PPA caused the vasculitis. It is, rather, the observation of a phenomenon that apparently follows, not precedes, a hemorrhagic stroke.

The results of this assessment of whether or not the relationship between PPA single ingredient diet aid use and hemorrhagic stroke is causal demonstrate that none of the five criteria evaluated (coherence, consistency, timing, specificity, and strength) are clearly satisfied for a causal relationship to exist. The lack of a concise biological mechanism of action; inconsistencies in the circumstances and etiology of the event; wide variations in the elapsed time between dose and event; the lack of a clear dose/effect response; and the prevalence of other factors independent of PPA use that can potentiate hemorrhagic stroke; all add together to present a very muddled, potentially misleading picture of this relationship. The available information suggests that there is no reasonable evidence of a causal relationship between the use of PPA single ingredient diet aids and the occurrence of hemorrhagic stroke.

In summary, the results of this epidemiologic analysis suggest that use of PPA single ingredient diet aids does not place the 15-44 year old female dieter at greater risk of developing a hemorrhagic stroke than from the effects of other, potentially more prevalent factors.

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TABLE 1
ESTIMATED PPA SINGLE INGREDIENT DIET AID (SIDA) USE AMONG U.S. WOMEN 15-44 YEARS OF AGE

AGE	1982 POP(1) (000s)	1982 USE(2) (%)	1982 USERS (000s)	1984 POP(1) (000s)	1984 USE(3) (%)	1984 USERS (000s)	1989 POP(1) (000s)	1989 USE(4) (%)	1989 USERS (000s)	1982-89 AVG. USERS (000s)
15-19	9,708	19x12.2	223	9,231	30x10.1	277	8,721	100x6.8	594	365
20-24	10,810	19x16.7	346	10,626	30x13.7	436	9,334	100x9.2	859	547
25-29	10,359	19x14.4	280	10,694	30x14.2	460	10,834	100x9.3	1,008	583
30-34	9,410	19x14.4	254	9,887	30x14.2	425	11,058	100x9.3	1,028	569
35-39	7,937	19x12.2	183	8,535	30x10.7	273	9,890	100x8.9	880	445
40-44	6,346	19x12.2	146	7,052	30x10.7	226	8,588	100x8.9	764	379
15-44	54,570	19x13.9	1,419	56,025	30x12.5	2,129	58,425	100x8.8	5,133	2,888

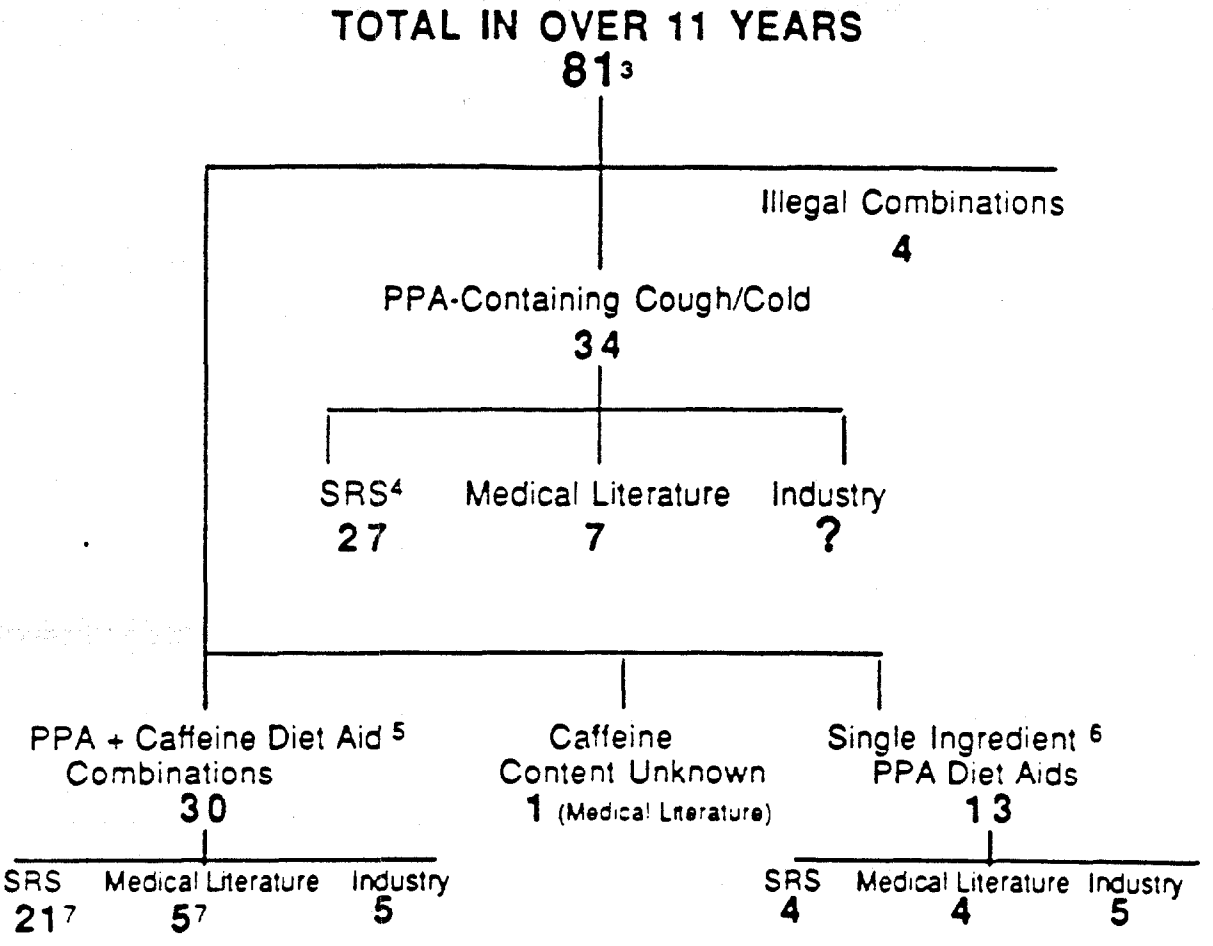
NOTES:

(1) Statistical Abstracts of the United States (1984, 1986 and 1990).
(2) 19% overall PPA SIDA shelf offtake volume (A.C. Nielsen, 1982) multiplied by % PPA diet aid use (Mediamark^{R}, 1982); 15-19 yr. old use extrapolated from 18-24 yr. old usage.
(3) 30% overall PPA SIDA shelf offtake volume (A.C. Nielsen, 1984) multiplied by % PPA diet aid use (Mediamark^{R}, 1984); 15-19 yr. old use extrapolated from 18-24 yr. old usage.
(4) 100% overall PPA SIDA shelf offtake volume (A.C. Nielsen, 1989) multiplied by % PPA diet aid use (Mediamark^{R}, 1989); 15-17 yr. old use determined by female teen market survey (1991).

a:appetit

TABLE 2

CEREBROVASCULAR HEMORRHAGES REPORTED TO BE ASSOCIATED WITH PPA USE (ALL SOURCES) AS REPORTED IN THE FDA SPONTANEOUS REPORTING SYSTEM[1], MEDICAL LITERATURE, AND ADDITIONS FROM THE DIET PILL INDUSTRY[2], 1/80 2/91



[1]Includes entries miscoded, ie, not under Phenylpropanolamine.

[2]The FDA did not request the manufacturers of PPA-containing cough/cold products to supply unreported additional complaints.

[3]One case reported concurrent use of both a diet aid and a PPA-containing cough/cold product.

[4]FDA Spontaneous Reporting System.

[5]PPA-containing diet aid products **NOT** currently available to the US consumer, and **NOT** manufactured after 1983.

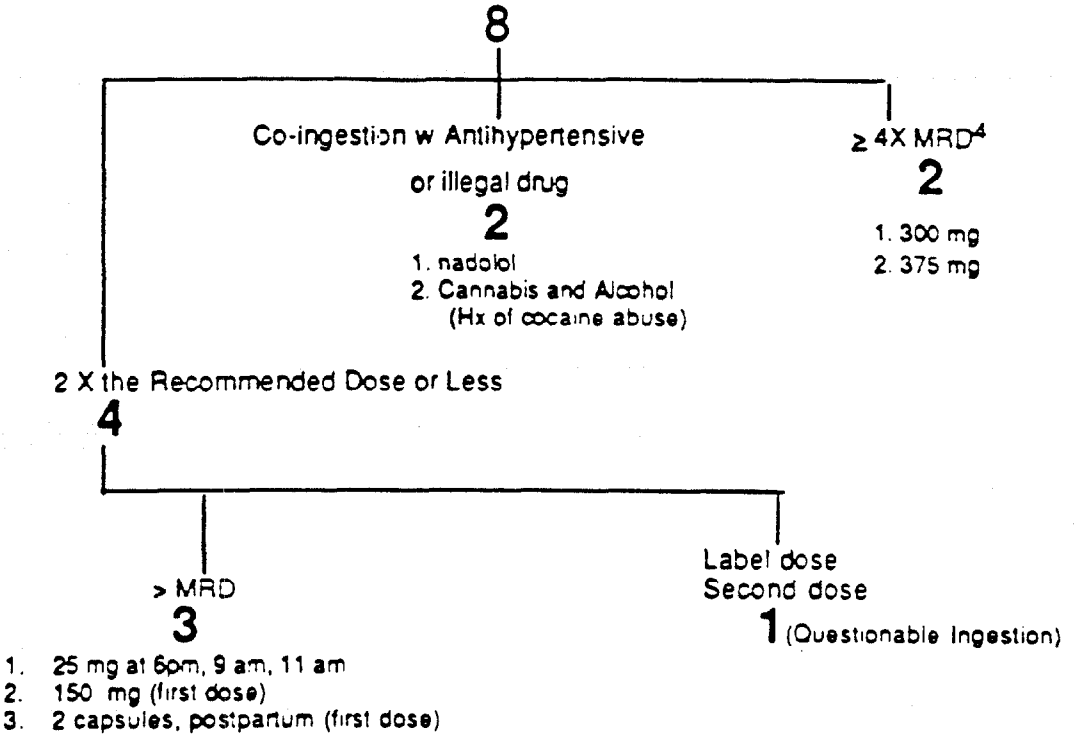
[6]PPA-containing diet aid products currently available to the US consumer.

[7]Case 83050103600101 (00160598) in the SRS was published in Kikta et al, *Stroke* 16: 510-512, 1985.

TABLE 3

CEREBROVASCULAR HEMORRHAGES REPORTED TO BE ASSOCIATED WITH SINGLE INGREDIENT PPA DIET AIDS[1] AS REPORTED IN THE FDA SPONTANEOUS REPORTING SYSTEM[2,3], MEDICAL LITERATURE, AND REPORTS FROM INDUSTRY 1980 - 2/91

FEMALES 15-44 YEARS



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[1]PPA-containing diet aid products currently available to the US consumer.
[2]Includes entries miscoded, ie, not included under Phenylpropanolamine
[3]Following review of the 1639s.
[4]MRD = maximum recommended dose.

TABLE 4
Numbers of Published and Unpublished Reports of Hemorrhagic Stroke Purportedly Associated with PPA Diet Aid Use by Females 15-44 Years of Age

Number of Reports for PPA Single Ingredient Diet Aids (All Reports)

	AGE GROUP						
YEAR	15-19	20-24	25-29	30-34	35-39	40-44	TOTAL
1980	0	0	0	0	0	0	0
1981	0	0	0	0	0	0	0
1982	0	0	0	1	0	0	1
1983	0	0	0	0	0	0	0
1984	0	0	0	0	0	0	0
1985	0	0	0	0	1*(H)	0	1
1986	0	1*(C)	0	0	0	1*	2
1987	1**	1***	1*	0	0	0	3
1988	0	0	0	1++	0	0	1
1989	0	0	0	0	0	0	0
1990	0	0	0	0	0	0	0
1980-90 Total	1**	2 (1*,1***)	1*	2	1*	1*	8

NOTES:

1. Sources: FDA SRS, medical literature, and company databases.

2. * = possible first dose event; ** = overdose; *** = overdose and possible first dose event; (H) = concomitant beta-blocker use; (C) = cocaine user; + = caffeine content unknown, but presumed to be zero; ++ = PPA ingestion not verified, but assumed.

a:numbrs

TABLE 5

RATE ESTIMATES OF HEMORRHAGIC STROKE (ICD CODES 430-432) FOR U.S. FEMALES AGE 15-44, 1979-88* DERIVED FROM THE NHDS

(RATE PER 100,000 POPULATION PER YEAR)

AGE	1979	1980	1982	1983	1984	1985	1986	1987	1988	TOTAL RATE 1979-80, 1982-88
15-19	2.35	4.31	0.32	0.00	4.99	0.87	4.31	0.00	1.00	2.04
20-24	6.35	4.67	1.01	0.00	1.48	2.23	1.26	4.96	4.29	2.88
25-29	4.40	0.00	3.06	9.98	8.22	12.19	0.27	2.86	7.35	5.42
30-34	17.96	14.71	17.18	1.73	5.38	3.62	10.56	9.19	12.79	10.18
35-39	10.39	14.05	8.25	28.65	10.26	9.05	16.80	5.29	11.13	12.56
40-44	17.93	16.19	7.76	11.65	19.09	19.32	21.96	28.87	36.51	20.64

*1981 hospitalization data were not available on computer tapes for public use.
Hospitalization data obtained from the National Hospital Discharge Survey

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TABLE 6
Background Rate and Expected Numbers of Hemorrhagic
Strokes in U.S. Female 15-44 Year Old PPA Single Ingredient Diet Aid Users

Age Group	Annual Rate Per 100,000[1]	Annual Person-Year Exposure Among the Diet Aid User Population (000s)[2] Days of Exposure/Year 365	33	2	Expected Number of Hemorrhagic Strokes Over 11 Years Assuming: 33 Multiple Exposures/Year[3]	Two First Dose Exposures/Year[4]
15-19	2.04	365	33.0	2.0	7	0.4
20-24	2.88	547	49.5	2.9	16	1
25-29	5.42	583	52.7	3.2	31	2
30-34	10.18	569	51.4	3.1	58	3
35-39	12.56	445	40.2	2.4	56	3
40-44	20.64	379	34.3	2.1	78	5
15-44	8.21	2888	261.1	15.8	246	14

Notes:

1. Nine-year average age-sex specific rates estimated from the National Hospital Discharge Survey for the years 1979, 1980, and 1982 through 1988. Rates were derived from NHDS estimates of discharges for ICD Code Nos. 430 (subarachnoid hemorrhage), 431 (intracerebral hemorrhage), and 432 (other and unspecified intracranial hemorrhage).

2. Estimated from Mediamark^{R} market survey data for 1982, 1984, and 1989 (see Table 1). Numbers are person-year exposures adjusted to 33 exposures/year and 2 exposures/year.

3. Assumes total of 33 days/year of PPA diet aid use (2 periods of use/year of 16.5 days/period based on market research). Annual number of strokes was multiplied by eleven to derive 11 year total.

4. Assumes two first-dose exposures/year from PPA diet aid use. Annual number of strokes was multiplied by eleven to derive 11 year total.

TABLE 7

NHDS-DERIVED RATES OF ICD CODES 430-432 IN U.S. FEMALE POPULATION COMPARED TO RATES OF ICD CODES 430-432 IN CANADIAN FEMALE POPULATION*

U.S. RATES FOR 430-432 (per 100,000)

AGE	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	TOTAL RATE 1979-80, 1982-88
15-19	2.35	4.31	N/A	0.32	0.00	4.99	0.87	4.31	0.00	1.00	2.04
20-24	6.35	4.67	N/A	1.01	0.00	1.48	2.23	1.26	4.96	4.29	2.88
25-34	11.20	7.02	N/A	9.86	6.08	6.88	8.04	5.28	5.98	10.07	7.77
35-44	15.27	15.03	N/A	8.03	20.92	14.15	13.61	19.05	16.04	22.80	16.31

CANADIAN RATES FOR 430-432 (per 100,000)

AGE	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	TOTAL RATE 1979-88
15-19	2.23	1.21	3.71	2.74	2.00	3.50	1.14	2.44	2.47	2.06	2.19
20-24	3.70	4.95	5.39	3.99	4.38	3.70	3.56	4.25	5.24	3.54	4.14
25-34	8.11	8.64	10.62	9.36	8.97	6.85	8.28	8.67	7.72	8.55	8.35
35-44	17.94	19.64	18.97	17.90	19.95	17.03	18.15	16.87	16.98	16.23	17.76

*Source: Hospital Morbidity Statistics, Canadian Center for Health Information (Ottawa), Statistics Canada

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TABLE 8
COMPARABILITY OF NHDS-DERIVED HEMORRHAGIC STROKE RATES TO RATES REPORTED FOR OTHER U.S. AND FOREIGN DATABASES
(RATE/100,000)

	STUDY	NHDS	NAT'L STROKE SURVEY	STOCKHOLM SWEDEN	GOTHENBURG SWEDEN	FLORENCE ITALY	AUCKLAND NEW ZEALAND	FINLAND	ROCHESTER MN	ROCHESTER MN	ICELAND
BARACHNOID HORRHAGE	YEAR	1979-88	1975-76	1973-77	1970-75	1983-85	1981/3	1966-72	1955-69[2]	1984[1,2]	1958-68
D CODE NO. 430)	REF#		33	43	43	44	45	46	34		47
F 0-35											3.3
F 0-34									1.6		
F 15-44		4.4	2.1	10.0	5.0	3.2		25.9			
F 35-44							18.9		13.7		
0-34											3.0
0-44		3.7	2.4								
15-24							0.7				
15-34						0.8					
15-44		5.2						16.8		6.0	
25-34				7.2			5.3				
35-44				17.2		7.5	21.5		10.6		
TRACEREBRAL HORRHAGE											
D CODE NO. 431)							N/A				
F 0-35											1.7
F 0-34									0.2		
F 15-44		3.2	0.7	5.0	3.0	1.9		13.6			
F 35-44									3.0		
0-34											1.6
0-44		2.0	0.8								
15-24											
15-34						0.7					
15-44		2.4						9.6		0.5	
25-34			2.1								
35-44			5.4			4.0			2.3		

TES:

Letter from J. Whisnant, M.D. (Mayo Clinic) to A. Ostfeld, M.D. (Yale University) dated 6/18/91

Incidence reported per 100,000 person-years.

TABLE 9
Comparison of Numbers of Observed Reports of Hemorrhagic Stroke Purportedly Associated with PPA Single Ingredient Diet Aids to Expected Number of Hemorrhagic Strokes in U.S. Females 15-44 Years of Age-Multiple Dose Risk Assumption (All Reports)

Age Group	1980-1990 Total Observed Reports[1]	1980-1990 Total Expected Strokes[2]
15-19	1	7
20-24	2	16
25-29	1	31
30-34	2	58
35-39	1	56
40-44	1	78
Total 15-44	8	246

Ratio[3] of Observed: Expected = 8/246 = 0.03
Ratio[3] (assuming 1 in 10 PER underreporting) of Observed: Expected = 80/246 = 0.33

NOTES:

1. Derived from FDA SRS, medical literature, and company PER databases.

2. Derived by assuming 33 days/yr exposure, and applying NHDS-derived hemorrhagic stroke rate to adjusted person-days of exposure among the 15-44 year old female PPA single ingredient diet aid user population to obtain expected number of hemorrhagic strokes for 33 days/year. This number is then multiplied by eleven to obtain 1980-1990 total expected strokes.

3. Morbidity ratio = number of observed hemorrhagic stroke reports - expected number of hemorrhagic strokes.

4. PER = Product Experience Report.

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TABLE 10

Comparison of Numbers of Observed Reports of Hemorrhagic Stroke Purportedly Associated with PPA Single Ingredient Diet Aids to Expected Number of Hemorrhagic Strokes in U.S. Females 15-44 Years of Age - Multiple Dose Risk Assumption (All Reports Minus Cases of Overdose and/or Contraindicated Medications or Conditions of Use)

Age Group	1980-1990 Total Observed Reports[1]	1980-1990 Total Expected Strokes[2]
15-19	0	7
20-24	0	16
25-29	1	31
30-34	2	58
35-39	0	56
40-44	1	78
Total 15-44	4	246

Ratio[3] of Observed: Expected = 4/246 = 0.02

Ratio[3] (assuming 1 in 10 PER underreporting) of Observed: Expected = 40/246 = 0.16

NOTES:

1. Derived from FDA SRS, medical literature, and company PER databases.

2. Derived by assuming 33 days/yr exposure, and applying NHDS-derived hemorrhagic stroke rate to adjusted person-days of exposure among the 15-44 year old female PPA single ingredient diet aid user population to obtain expected number of hemorrhagic strokes for 33 days/year. This number is then multiplied by eleven to obtain 1980-1990 total expected strokes.

3. Morbidity ratio = number of observed hemorrhagic stroke reports - expected number of hemorrhagic strokes.

4. PER = Product Experience Report.

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TABLE 11
Comparison of Numbers of Observed Reports of Hemorrhagic Stroke Purportedly Associated with PPA Single Ingredient Diet Aids to Expected Number of Hemorrhagic Strokes in U.S. Females 15-44 Years of Age-First Dose Risk Assumption (All Reports)

Age Group	1980-1990 Total Observed Reports[1]	1980-1990 Total Expected Strokes[2]
15-19	0	0.4
20-24	2	1
25-29	1	2
30-34	0	3
35-39	1	3
40-44	1	5
Total 15-44	5	14

Ratio[3] of Observed: Expected = 5/14 = 0.36
Ratio[3] (assuming 1 in 10 PER underreporting) of Observed: Expected = 50/14 = 3.57

NOTES:

1. Derived from FDA SRS, medical literature, and company PER databases.

2. Derived by assuming 2 days/yr exposure, and applying NHDS-derived hemorrhagic stroke rate to adjusted person-days of exposure among the 15-44 year old female PPA single ingredient diet aid user population to obtain expected number of hemorrhagic strokes for 2 days/year. This number is then multiplied by eleven to obtain 1980-1990 total expected strokes.

3. Morbidity ratio = number of observed hemorrhagic stroke reports - expected number of hemorrhagic strokes.

4. PER = Product Experience Report.

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TABLE 12

Comparison of Numbers of Observed Reports of Hemorrhagic Stroke Purportedly Associated with PPA Single Ingredient Diet Aids to Expected Number of Hemorrhagic Strokes in U.S. Females 15-44 Years of Age-First Dose Risk Assumption (All Reports Minus Cases of Overdose and/or Contraindicated Medications or Conditons of Use)

Age Group	1980-1990 Total Observed Reports[1]	1980-1990 Total Expected Strokes[2]
15-19	0	0.4
20-24	0	1
25-29	1	2
30-34	0	3
35-39	0	3
40-44	1	5
Total 15-44	2	14

Ratio[3] of Observed: Expected = 2/14 = 0.14

Ratio[3] (assuming 1 in 10 PER underreporting) of Observed: Expected = 20/14 = 1.43

NOTES:

1. Derived from FDA SRS, medical literature, and company PER databases.

2. Derived by assuming 2 days/yr exposure, and applying NHDS-derived hemorrhagic stroke rate to adjusted person-days of exposure among the 15-44 year old female PPA single ingredient diet aid user population to obtain expected number of hemorrhagic strokes for 2 days/year. This number is then multiplied by eleven to obtain 1980-1990 total expected strokes.

3. Morbidity ratio = number of observed hemorrhagic stroke reports - expected number of hemorrhagic strokes.

4. PER = Product Experience Report.

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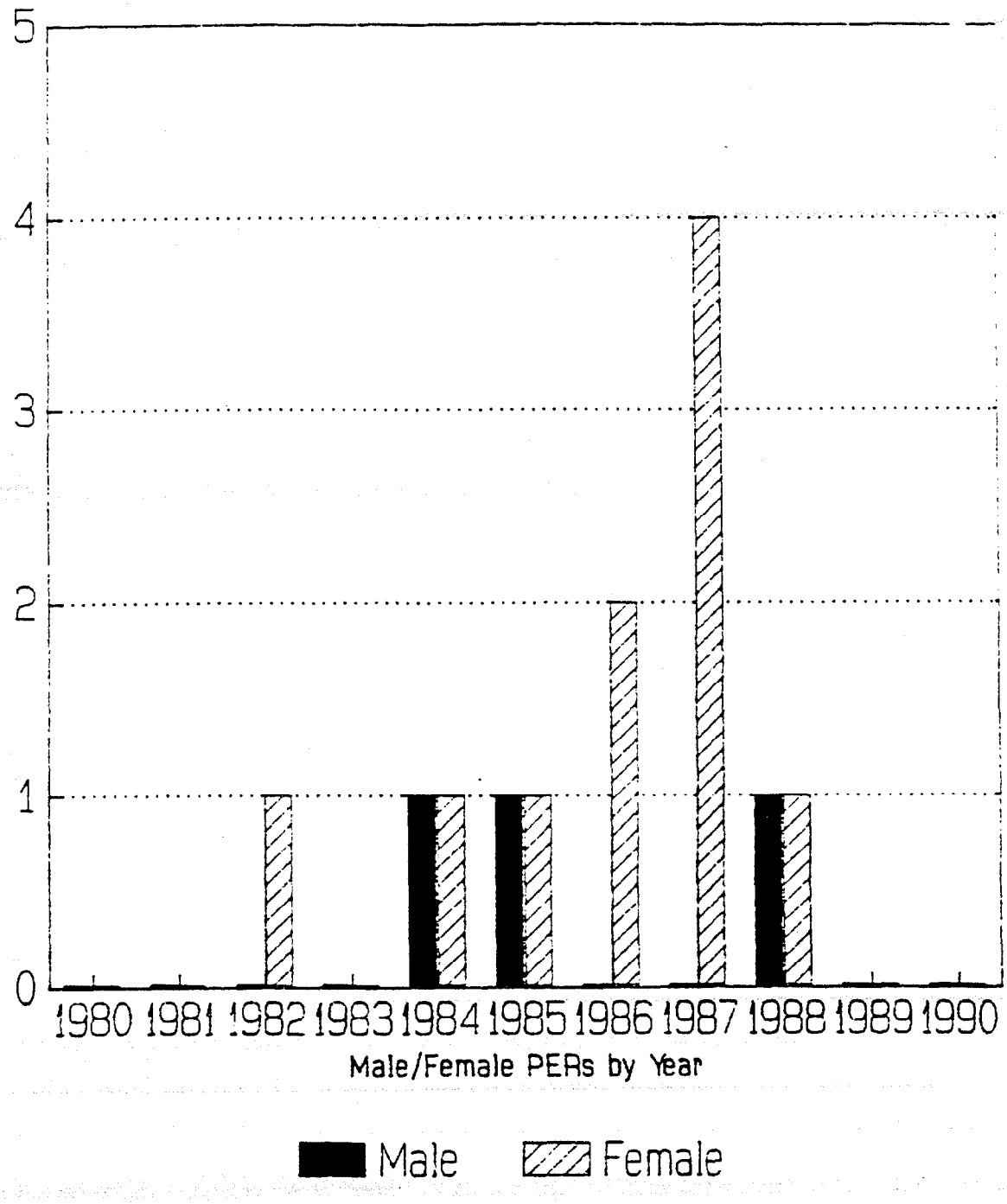
Figure 1

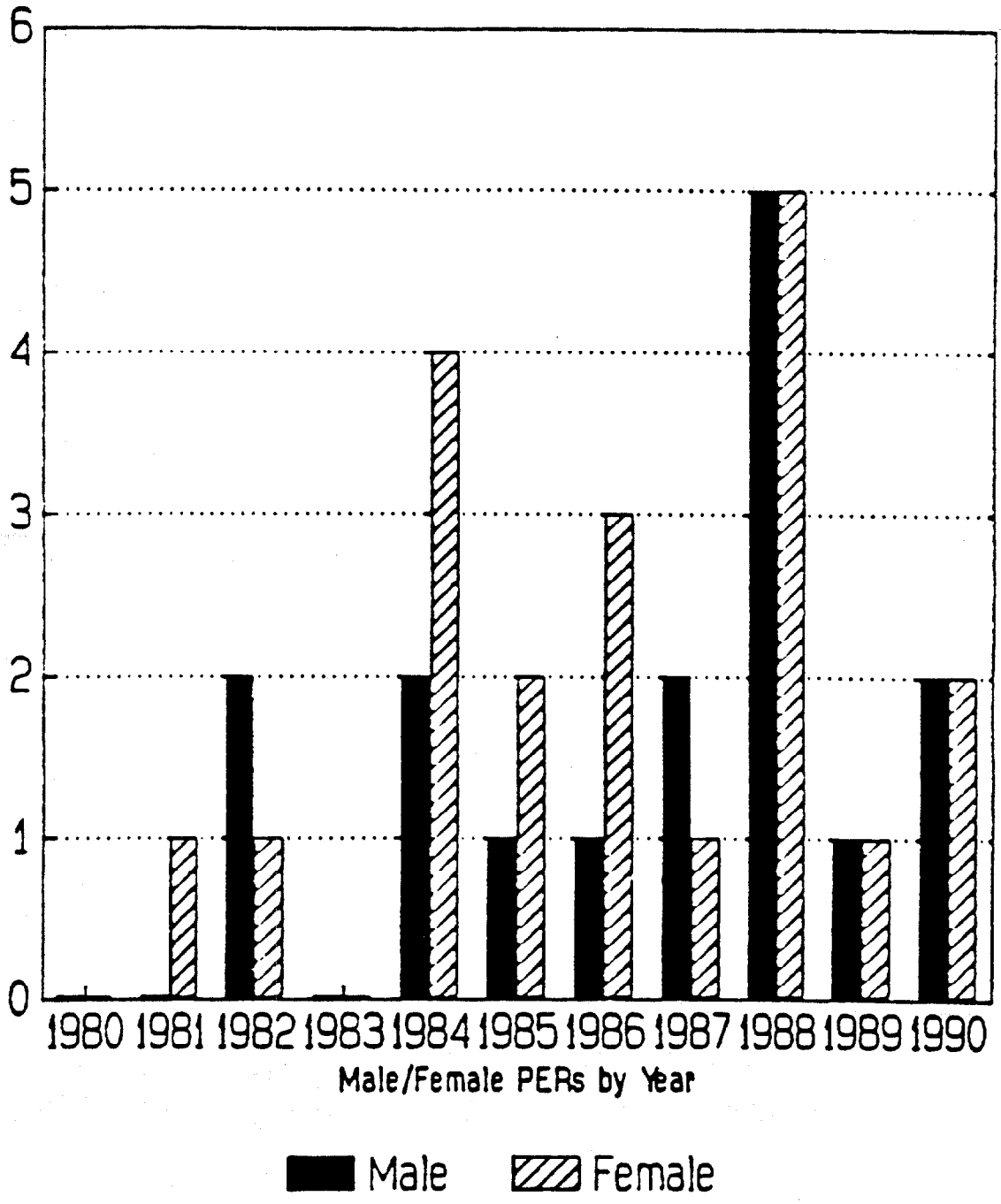
Hemorrhagic Stroke PERs Associated with
PPA Single Ingredient Diet Aid Use



(All Reports)

FIGURE 2

Hemorrhagic Stroke PERs Associated with PPA Cough/Cold Product Use (All Reports)



(sex unk for 1981 PER; assumed female)

FIGURE 3

Hemorrhagic Stroke PERs Associated with PPA Drug Product Use (All Reports)

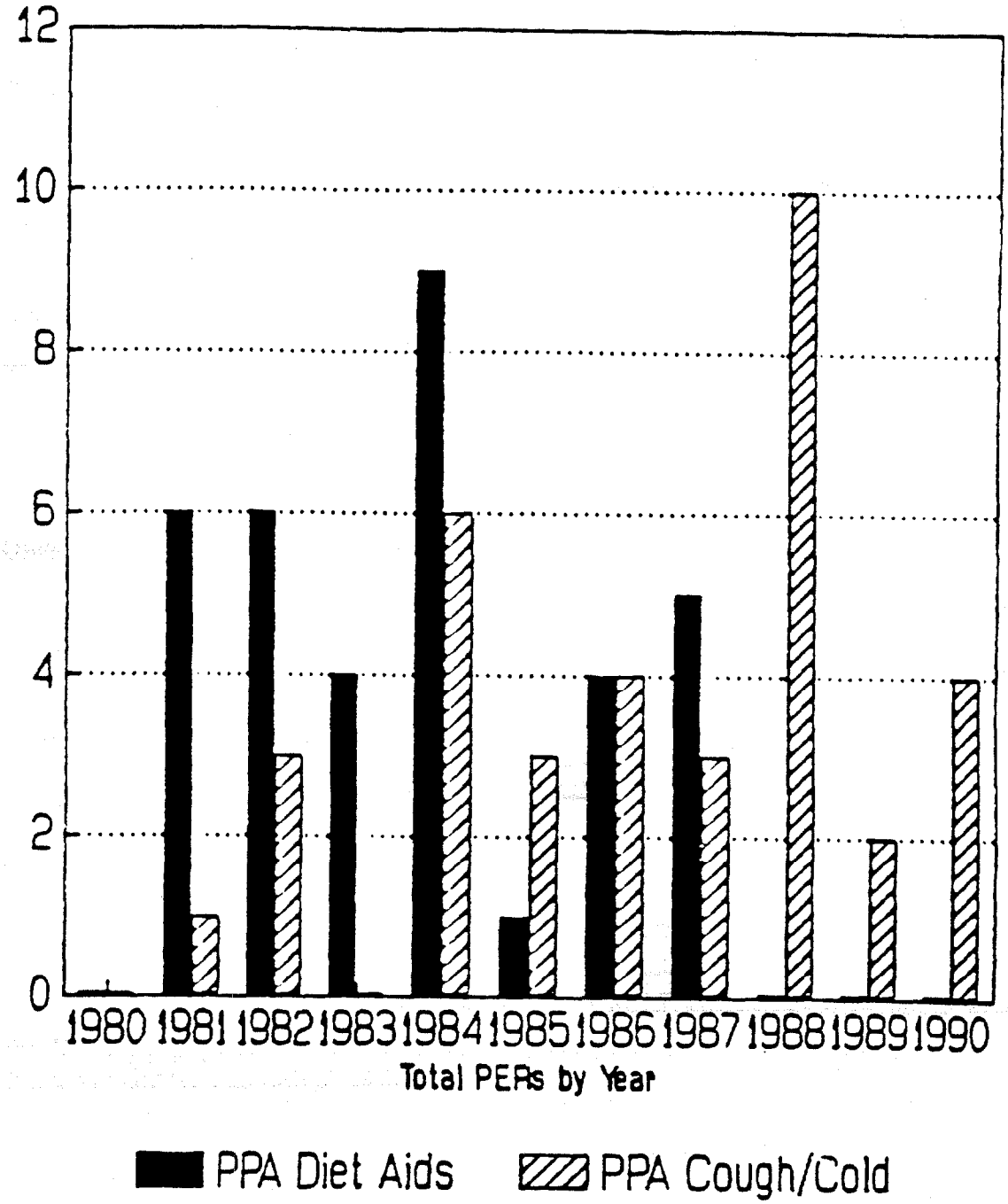


FIGURE 4

COMPARABILITY OF U.S. NHDS-DERIVED RATES TO
CANADIAN RATES OF HEMORRHAGIC STROKE IN FEMALES

FEMALES 15-19 YEARS OF AGE

⊡ = U.S. POPULATION (FROM NHDS)

⊙ = CANADIAN POPULATION

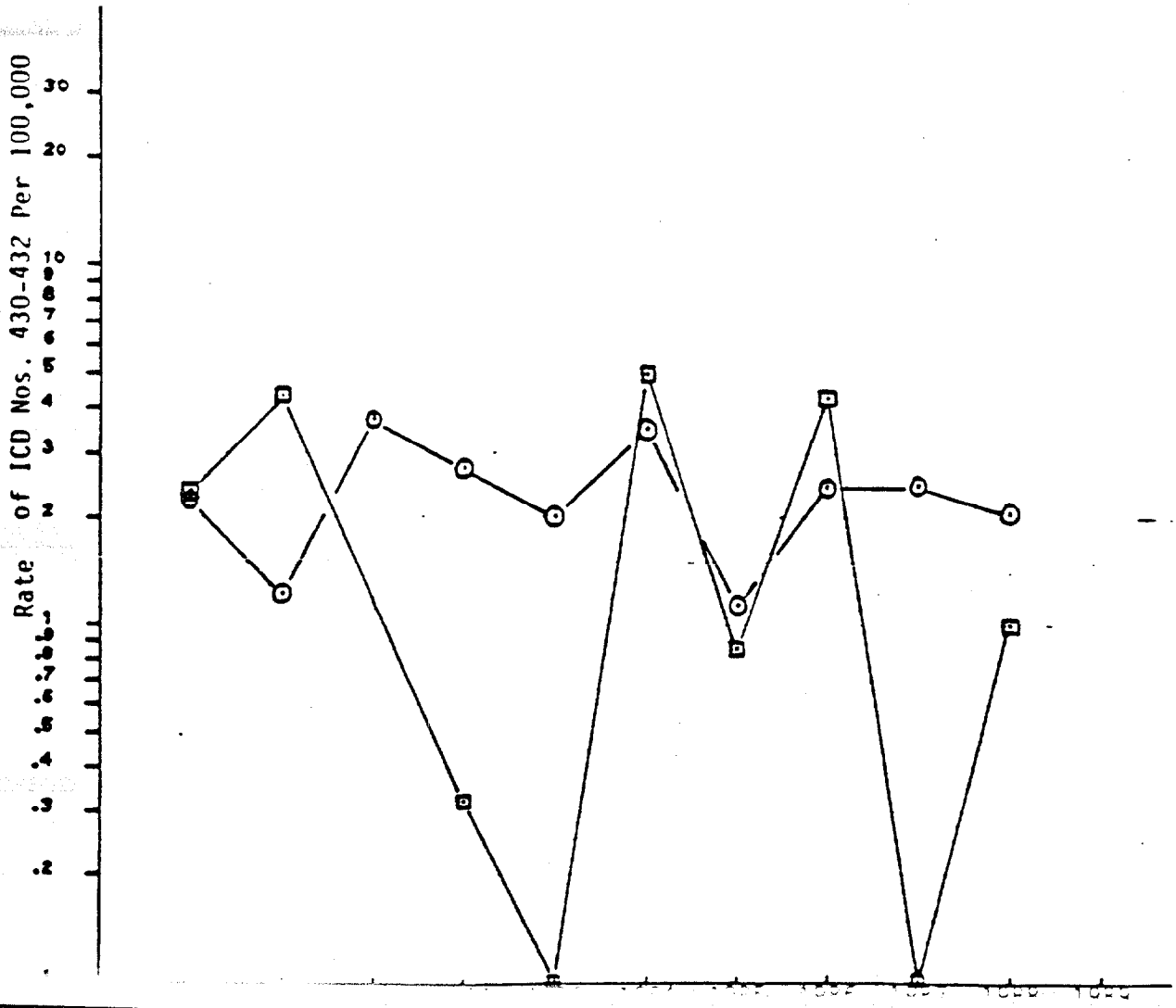


FIGURE 5

COMPARABILITY OF U.S. NHDS-DERIVED RATES TO
CANADIAN RATES OF HEMORRHAGIC STROKE IN FEMALES

FEMALES 20-24 YEARS OF AGE

⊡ = U.S. POPULATION (FROM NHDS)

⊙ = CANADIAN POPULATION

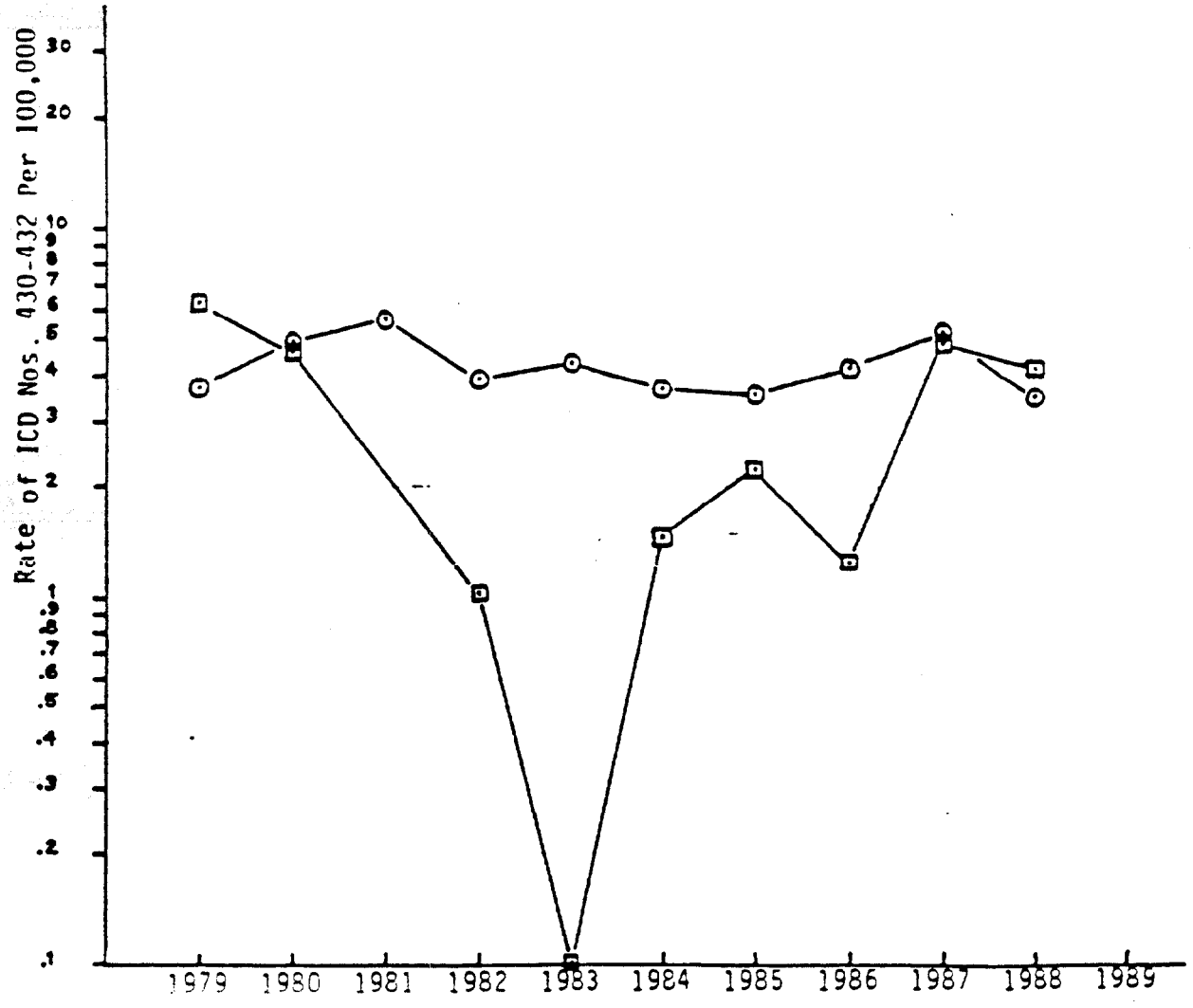


FIGURE 6

COMPARABILITY OF U.S. NHDS-DERIVED RATES TO
CANADIAN RATES OF HEMORRHAGIC STROKE IN FEMALES

FEMALES 25-34 YEARS OF AGE

⊡= U.S. POPULATION (FROM NHDS)

⊙= CANADIAN POPULATION

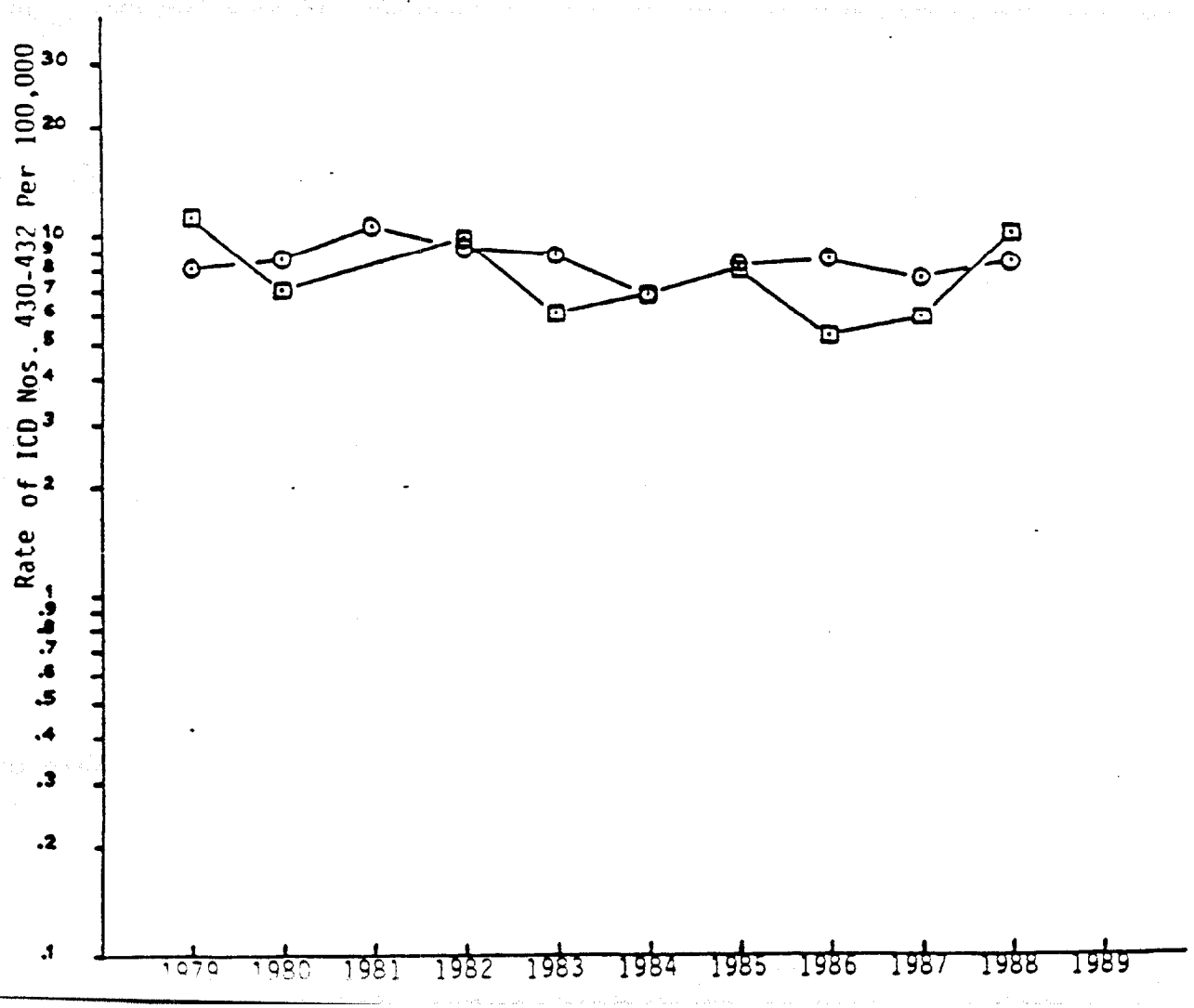


FIGURE 7

COMPARABILITY OF U.S. NHDS-DERIVED RATES TO
CANADIAN RATES OF HEMORRHAGIC STROKE IN FEMALES

FEMALES 35-44 YEARS OF AGE

⊡= U.S. POPULATION (FROM NHDS)

⊙= CANADIAN POPULATION