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UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

IN RE: PHENYLPROPANOLAMINE
(PPA) PRODUCTS LIABILITY
LITIGATION,

MDL NO. 1407

This document relates to all
actions

ORDER GRANTING IN PART
AND DENYING IN PART MDL
DEFENDANTS' MOTION TO
PRECLUDE PLAINTIFFS'
EXPERT OPINIONS AS TO
GENERAL CAUSATION
PURSUANT TO FED. R. EVID.
702 AND 703 AND DAUBERT

cc: counsel: VBTK

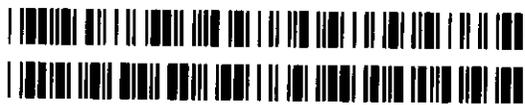
I. INTRODUCTION

Defendants in this multi-district litigation filed a motion to preclude plaintiffs' expert opinions as to general causation pursuant to Federal Rules of Evidence 702 and 703 and Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579 (1993). Having reviewed pleadings filed in support of and in opposition to the motion, along with the remainder of the record, and having heard oral argument and expert testimony, and, being fully advised, the court finds and concludes as follows:

II. BACKGROUND

A. Regulatory History of PPA

Phenylpropanolamine ("PPA") was first synthesized in the early 1900s. As a sympathomimetic drug, PPA mimics aspects of



1892

1 the sympathetic nervous system. By the 1970s, PPA was widely
2 used in over-the-counter ("OTC") and prescription cough and cold
3 and appetite suppressant products.

4 Because its commercial use predated the Food and Drug
5 Administration's ("FDA") adoption of rules and procedures govern-
6 ing the sale of OTC products, the FDA "grandfathered" PPA into
7 the system. Pursuant to a monograph review process initiated in
8 1972, the FDA intended to categorize PPA and other grandfathered
9 drugs as either "generally recognized," "not generally recog-
10 nized," or "insufficient data to permit classification" - as safe
11 and effective. The FDA allowed grandfathered drugs to remain on
12 the market until a final rule issued.

13 In 1976, an FDA advisory review panel recommended the
14 categorization of PPA-containing cough and cold products as
15 generally recognized as safe and effective. A similar recommen-
16 dation for PPA-containing appetite suppressant products followed
17 in 1982. However, despite ongoing consideration of the safety of
18 these products, the FDA never formally categorized PPA.

19 B. Reports and Studies Addressing Safety of PPA

20 1. Early Reports and Studies:

21 From the 1970s on, case reports, case series, and medical
22 literature addressed adverse effects purportedly associated with
23 PPA. Beginning in 1979, more than thirty published case reports
24 described the occurrence of hemorrhagic stroke following the
25 ingestion of PPA. Many of these reports involved adolescent
26 girls and women utilizing PPA-containing appetite suppressants.

1 Also, some animal studies and human clinical trials demonstrated
2 sudden increases in blood pressure in response to PPA.

3 2. Early Epidemiological Studies:

4 A 1984 epidemiological study examined the occurrence of
5 cerebral hemorrhage in patients filling a PPA prescription. The
6 "Jick study," the results of which were published in a letter to
7 the editor, did not find a significant association between PPA
8 and hemorrhage stroke. The "O'Neill and Van de Carr study," an
9 unpublished study also conducted in the mid-1980s, reached a
10 similar conclusion based on analysis of computer profiles in two
11 states' medicaid databases.

12 3. Review of FDA's Spontaneous Reporting System:

13 In 1991, Dr. Heidi Jolson, an FDA epidemiologist, reviewed
14 the FDA's Spontaneous Reporting System ("SRS") database for
15 cerebrovascular accidents and hypertensive episodes reported in
16 association with PPA ingestion. Jolson found that, between 1969
17 and 1991, the FDA received twenty-nine spontaneous reports of
18 cerebrovascular accidents associated with PPA, twenty-two of
19 which involved hemorrhagic stroke associated with PPA in appetite
20 suppressants (16 cases) and cough and cold products (6 cases).
21 She found the data suggested that PPA-containing diet pills
22 increase the risk of cerebrovascular accidents.

23 4. The Yale Hemorrhagic Stroke Project:

24 Following Dr. Jolson's SRS study, the Nonprescription Drug
25 Manufacturers Association ("NDMA") and several drug manufacturers
26 initiated discussions with scientists from Yale University

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1 regarding an epidemiological study investigating links between
2 PPA and hemorrhagic stroke. In 1992, the FDA, NDMA, Yale scien-
3 tists, and two PPA product manufacturers who agreed to sponsor
4 the study collaborated in the design of the Hemorrhagic Stroke
5 Project ("HSP"). A Scientific Advisory Group ("SAG") operated
6 autonomously from the investigators and sponsors to provide
7 general oversight throughout the study. In 1994, all involved
8 entities approved the study protocol.

9 As a "case-control" study, the HSP sought to compare PPA
10 exposure in individuals who suffered hemorrhagic strokes (the
11 "cases") and those who did not suffer hemorrhagic strokes (the
12 "controls"). The study limited itself to men and women between
13 the ages of eighteen and forty-nine.

14 The HSP aimed to estimate: (1) among men and women, the
15 association between "any use" of PPA and hemorrhagic stroke; (2)
16 among men and women, the association between PPA and hemorrhagic
17 stroke by type of exposure (cough/cold or appetite suppression);
18 and (3) among women (a) the association between "first use" of
19 PPA and hemorrhagic stroke and (b) the association between PPA in
20 appetite suppressants and hemorrhagic stroke. "Any use" included
21 use within the three days preceding the "focal time," defined as
22 the onset of symptoms plausibly related to the stroke and causing
23 the patient to seek medical attention. "First use" meant that an
24 individual consumed the product within twenty-four hours before
25 the focal time, with no other use in the preceding two weeks.

26 The HSP issued its final report in May 2000. The HSP

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1 investigators construed the results of the study to suggest that
2 PPA increases the risk of hemorrhagic stroke. Among other
3 findings, the investigators found that, for women, the use of a
4 PPA-containing appetite suppressant was associated with an
5 increased risk of hemorrhagic stroke (16.58 odds ratio, lower
6 limit of one-sided 95% confidence interval ("LCL") = 2.22, p-
7 value = 0.011).¹ The investigators also found a suggestion of an
8 association in women with any first use of PPA, all of which
9 involved cough or cold products (3.13 odds ratio, LCL = 1.05, p-
10 value = 0.042). Because no men reported use of appetite suppres-
11 sants and only two reported first use of a PPA-containing prod-
12 uct, the investigators could not determine whether PPA posed an
13 increased risk for hemorrhagic stroke in men.

14 C. Withdrawal of PPA from the Market

15 In October 2000, the FDA convened a meeting of the Non-
16 prescription Drug Advisory Committee ("NDAC") to consider the
17 impact of the HSP. The NDAC recommended that PPA-containing
18 products no longer be available for OTC use.

19 On November 6, 2000, the FDA requested voluntary removal of
20 PPA-containing products from the market and issued a public
21 health advisory. Entities responsible for manufacturing and
22 marketing these products withdrew them from the market. In

23
24 ¹The odds ratio reflects the odds that a case was exposed to
25 the odds that a control was exposed. P-values measure the
26 probability that the reported association was due to chance,
while confidence intervals indicate the range of values within
which the true odds ratio is likely to fall.

1 December 2000, the New England Journal of Medicine ("NEJM")
2 published the HSP results in a lead article. See Walter N.
3 Kernan et al., Phenylpropanolamine and the Risk of Hemorrhagic
4 Stroke, 343 New Eng. J. Med. 1826 (2000) (hereinafter "NEJM
5 Article").

6 III. DISCUSSION

7 Plaintiffs' Steering Committee ("PSC") proffer fourteen
8 experts endorsing their general causation theory, including
9 experts in pharmacology, epidemiology, neurology, toxicology, and
10 pediatrics.² Defendants challenge the reliability of all of
11 plaintiffs' general causation expert opinions. They assert the
12 inadmissibility of these opinions to support a conclusion that
13 PPA can cause hemorrhagic stroke, ischemic stroke, cardiac
14 injuries, or, to the extent claims of this nature may exist,
15 seizures or psychoses. Defendants also focus on the parameters

16
17 ²The PSC-identified experts include: Dr. Jerome Avorn; Dr.
18 Rubin Richard Clapp; Dr. Robert A. Egan; Dr. Edward Feldmann; Dr.
19 Steven J. Kittner; Dr. Raymond C. Lake; Dr. James R. McDowell;
20 Dr. Walter Molofsky; Dr. Paul R. Pentel; Dr. George Ricaurte; Dr.
21 Stanley Turhim; Dr. Alan Woolf; and Dr. Gary P. Zaloga. Also,
22 although not originally designated as a PSC witness, the court
23 allowed Dr. Steven R. Levine to testify as to ischemic stroke
24 injuries. Individual plaintiffs also offer additional experts in
25 accordance with an order allowing designation of additional
26 general causation experts so long as their "opinions, evidence
and/or theories have not previously been determined by the Court
to be scientifically unreliable or otherwise inadmissible."
Stip. and Order Re: Expert Disclosures at 2 (Sept. 9, 2002). As
this order will control the scope of general causation testimony
permitted by any expert witness offered in any federal PPA
litigation, the court denies the motion, filed on behalf of
certain plaintiffs, to deem the Daubert objections waived as to
Dr. Donald Marks.

1 and results of the HSP, arguing that the study lacks reliability
2 as to certain "sub-populations," including men, individuals below
3 age eighteen and above age forty-nine, and individuals suffering
4 strokes more than three days after ingestion of PPA.

5 A. The Daubert Standard

6 Federal Rule of Evidence 702 governs the admissibility of
7 expert testimony. Pursuant to this rule, a witness qualified as
8 an expert in "scientific . . . knowledge" may testify thereto if
9 "(1) the testimony is based upon sufficient facts or data, (2)
10 the testimony is the product of reliable principles and methods,
11 and (3) the witness has applied the principles and methods
12 reliably to the facts of the case." Fed. R. Evid. 702.

13 As established by the Supreme Court in Daubert v. Merrell
14 Dow Pharms., Inc., 509 U.S. 579 (1993), a trial court acts as a
15 "gatekeeper" to the admission of expert scientific testimony
16 under Rule 702. The court must conduct a preliminary assessment
17 to "ensure that any and all scientific testimony or evidence
18 admitted is not only relevant, but reliable." Id. at 589. This
19 two-step assessment requires consideration of whether (1) the
20 reasoning or methodology underlying the testimony is scientifi-
21 cally valid (the "reliability" prong); and (2) whether that
22 reasoning or methodology properly can be applied to the facts in
23 issue (the "relevancy" prong). Id. at 592-93; Kennedy v.
24 Collagen Corp., 161 F.3d 1226, 1228 (9th Cir. 1998).

25 Reliable testimony must reflect "scientific knowledge" -
26 implying a "grounding in the methods and procedures of sci-

1 ence[,]” and signifying something beyond “subjective belief or
2 unsupported speculation.” Daubert, 509 U.S. at 590. The infer-
3 ences or assertions drawn by the expert must be “derived by the
4 scientific method.” Id. In essence, the court must determine
5 whether the expert’s work product amounts to “‘good science.’”
6 Daubert v. Merrell Dow Pharms., Inc., 43 F.3d 1311, 1315 (9th
7 Cir. 1995) (“Daubert II”) (quoting Daubert, 509 U.S. at 593)
8 The relevancy, or “fit,” prong requires that the testimony be
9 “‘relevant to the task at hand,’ . . . i.e., that it logically
10 advances a material aspect of the proposing party’s case.” Id.
11 (quoting Daubert, 509 U.S. at 597).³

12 In Daubert, the Supreme Court outlined factors relevant to
13 the reliability prong, including: (1) whether the theory can be
14 and has been tested; (2) whether it has been subjected to peer
15 review; (3) the known or potential rate of error; and (4) whether
16 the theory or methodology employed is generally accepted in the
17 relevant scientific community. 509 U.S. at 593-94. The Court
18 emphasized the “flexible” nature of this inquiry. Id. at 594.
19 As later confirmed in Kumho Tire Co. v. Carmichael, 526 U.S. 137,
20 141-42 (1999): “Daubert’s list of specific factors neither
21 necessarily nor exclusively applies to all experts or in every
22 case. Rather, the law grants a district court the same broad

23
24 ³ Defendants appear to focus exclusively on Daubert’s
25 reliability prong. Given that each of plaintiffs’ expert
26 opinions would assist the trier of fact in reaching a conclusion
as to general causation, the court finds the relevancy prong of
Daubert satisfied. See, e.g., Kennedy, 161 F.3d at 1230.

1 latitude when it decides how to determine reliability as it
2 enjoys in respect to its ultimate reliability determination."
3 Accord Daubert II, 43 F.3d at 1317 ("[W]e read the Supreme Court
4 as instructing us to determine whether the analysis undergirding
5 the experts' testimony falls within the range of accepted stan-
6 dards governing how scientists conduct their research and reach
7 their conclusions.")

8 The Daubert analysis focuses on the principles and methodol-
9 ogy underlying an expert's testimony, not on the expert's conclu-
10 sions. 509 U.S. at 595. However, the Supreme Court later
11 cautioned that "conclusions and methodology are not entirely
12 distinct from one another." General Elec. Co. v. Joiner, 522
13 U.S. 136, 146 (1997). As such, "[a] court may conclude that
14 there is simply too great an analytical gap between the data and
15 the opinion proffered." Id. (finding nothing in either Daubert
16 or the Federal Rules of Evidence requiring the admission of
17 opinion evidence connected to existing data "only by the *ipse*
18 *dixit* of the expert.")

19 Upon remand of Daubert, the Ninth Circuit added that expert
20 testimony "based directly on legitimate, preexisting research
21 unrelated to the litigation provides the most persuasive basis
22 for concluding that the opinions[] expresse[d] were 'derived by
23 the scientific method.'" Daubert II, 43 F.3d at 1317. Where not
24 based on independent research, the testimony must be supported by
25 objective, verifiable evidence that it rests on scientifically
26 valid principles, such as peer review and publication in a

1 reputable scientific journal. Id. at 1317-18. In the absence of
2 independent research or peer review, experts must explain the
3 process by which they reached their conclusions and identify some
4 type of objective source demonstrating their adherence to the
5 scientific method. Id. at 1318-19; Domingo v. T.K., 289 F.3d
6 600, 605-06 (9th Cir. 2002).

7 B. Defendants' Daubert Challenges

8 1. Seizures, Psychoses, and Injuries Occurring More than
9 Three Days After Ingestion of PPA:

10 The court held a one-day informational hearing in which the
11 parties presented their arguments on defendants' motion. Follow-
12 ing that hearing, the court issued preliminary rulings, narrowing
13 the scope of the subsequent Daubert hearings. See Prelim. Ruling
14 on Defs.' Mot. to Preclude Pls.' Ex. Op's (Apr. 4, 2003); Order
15 Re: Apr. 7, 2003 Status Conf. (Apr. 8, 2003).

16 The court found insufficient basis to support expert testi-
17 mony as to injuries occurring more than three days after inges-
18 tion of PPA. All of the evidence and expert opinions proffered
19 support the HSP's three day window and plaintiffs did not inform
20 the court of an injury occurring outside that time frame.⁴ The
21 court finds the lack of supportive scientific evidence and
22 testimony dispositive.

23 The court also concluded that plaintiffs offered no scien-
24 tific basis for admitting expert opinions on seizures or psycho-

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26 ⁴ All plaintiffs were on notice that the court would
consider this and all of defendants' other Daubert challenges.

1 ses attributed to PPA. Again, no plaintiff pursued such a claim.
2 Also, the few expert opinions proffered with respect to these
3 injuries were no more than conclusory. Given the dearth of
4 supportive evidence, the court finds any opinions as to these
5 injuries scientifically unreliable.⁵

6 2. Hemorrhagic Stroke in Women Between the Ages of
7 Eighteen and Forty-Nine:

8 Hemorrhagic stroke results from the rupturing of a blood
9 vessel in the brain. The hemorrhage may be either intracerebral
10 (within the brain itself) or subarachnoid (within the fluid-
11 filled space surrounding the brain) (hereinafter "ICH" and "SAH"
12 respectively). Approximately fifteen to twenty percent of
13 strokes fall into the hemorrhagic category.

14 In supporting general causation between PPA and hemorrhagic
15 stroke, plaintiffs' experts base their opinions on several lines
16 of evidence, including: (1) the HSP; (2) the biological plausi-
17 bility for PPA to cause stroke, including evidence that PPA
18 causes (a) narrowing of cerebral blood vessels; (b) sudden spikes
19 in blood pressure; and (c) "beading" of arteries in the brain
20 (including the similarity of PPA to other drugs in the same class
21 known to have the same effect); (3) animal studies, (4) human
22 clinical studies; (5) case reports and case series; (6) medical
23 textbooks and other treatises; and (7) the SRS study.

24
25 ⁵ For the reasons described below, the court also issued a
26 preliminary ruling finding admissible the expert testimony based
on the HSP and related to hemorrhagic stroke in women from age
eighteen and above.

1 a. The HSP:

2 The HSP found an association between PPA and hemorrhagic
3 stroke in women between the ages of eighteen and forty-nine.
4 Defendants describe the HSP investigators' use of a one-tailed
5 statistical analysis⁶ as unconventional, and identify numerous
6 perceived flaws, many of which they maintain were unknown to the
7 FDA and/or NEJM.⁷ They identify the finding relating to women
8 and appetite suppressants as the only statistically significant
9 result after peer review, and note that even that number resulted
10 from a mere six cases in comparison to one control. Defendants
11 maintain the insufficiency of a "suggestion of an association"
12 for first use/cough and cold products in women, and note that
13 this finding similarly rests on small numbers, including no more
14 than seven cases and four controls.

15 Courts frequently depend on epidemiologic studies in deter-
16 mining the reliability of expert testimony. See 2 Modern Scien-
17 tific Evidence: The Law and Science of Expert Testimony § 28-1.1,
18 at 302-03 (David L. Faigman et al. eds., 1997) ("Epidemiologic
19 studies have been well received by courts trying mass tort suits.
20 Well-conducted studies are uniformly admitted. The widespread

21
22 ⁶A one-tailed test looks only to whether an agent increases
23 the risk, while a two-tailed test also looks to whether an agent
protects against the risk.

24 ⁷Those flaws include fragile data, improper use of random
25 digit dialing, low participation by eligible controls, chance,
26 temporal precedence bias, misclassification bias, selection bias,
inadequate adjustments for confounding, the combination of ICH
and SAH, and various protocol violations and errors.

1 acceptance of epidemiology is based in large part on the belief
2 that the general techniques are valid.") See also Daubert, 509
3 U.S. at 593 ("Ordinarily, a key question to be answered in
4 determining whether a theory or technique is scientific knowledge
5 that will assist the trier of fact will be whether it can be (and
6 has been) tested.") Despite the many and varied concerns raised
7 by defendants in regard to the HSP, the court finds, pursuant to
8 Daubert, testimony relying on this study reliable, especially
9 when taken in conjunction with the additional lines of evidence
10 addressed below.

11 Significantly, the HSP grew out of pre-litigation research
12 and was subjected to peer review. Daubert II, 43 F.3d at 1318
13 ("Establishing that an expert's proffered testimony grows out of
14 pre-litigation research or that the expert's research has been
15 subjected to peer review are the two principal ways the proponent
16 of expert testimony can show that the evidence satisfies the
17 first prong of Rule 702.") Plaintiffs' roster of experts include
18 a co-investigator/co-author of the HSP, as well as a participant
19 in the October 2000 FDA NDAC meeting convened to consider the
20 impact of the study. See Defs.' Exs. A-5 and A-6 (expert reports
21 of Drs. Edward Feldmann and Steven J. Kittner). The prestigious
22 NEJM published the HSP results, further substantiating that the
23 research bears the indicia of good science. See Daubert II, 43
24 F.3d at 1318 ("That the research is accepted for publication in a
25 reputable scientific journal after being subjected to the usual
26 rigors of peer review is a significant indication that it is

1 taken seriously by other scientists, i.e., that it meets at least
2 the minimal criteria of good science.”) (citing Daubert, 509
3 U.S. at 593 (“[S]crutiny of the scientific community is a compo-
4 nent of ‘good science[.]’”))

5 Even prior to submission to the NEJM, the HSP underwent
6 multiple layers of review. In addition to the FDA and the
7 autonomous SAG, the HSP involved, from its inception, both the
8 NDMA and two defendant-manufacturers. This involvement included
9 approval of the investigators selected, the SAG members, and the
10 study protocol, as well as an opportunity to challenge the study.

11 In fact, in reviewing the study and industry criticisms, the
12 FDA considered many of the same challenges raised here. In
13 rejecting these criticisms, the FDA epidemiologic and statistical
14 reviewers found the study “well designed and executed.” See FDA
15 Epid. Rev. (Sept. 27, 2000), Pls.’ Ex. D-9 at 1, 9; accord FDA
16 Stat. Rev. (Sept. 26, 2000), Pls.’ Ex. D-8 at 16.⁸ The
17 epidemiologists found the study’s strengths to include: “the
18 clarity of its objectives, the meticulous adherence to sound
19 epidemiology practices in its design and execution, and the
20 consistency of the findings, regardless of the analytic methods ”
21 See FDA Epid. Rev. at 9. Indeed, far from finding the study

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24 ⁸ The reviewers considered, inter alia, selection bias,
25 temporal precedence bias, misclassification bias, small sample
26 size and recruitment of controls, confounding, statistical
methodology, and “sparse data” bias. In rejecting these
concerns, the reviewers found that “[a]ll reasonable steps were
taken to minimize bias and confounding.” See FDA Epid. Rev. at 1.

1 flawed, the FDA's statistician found the HSP "one of the best
2 planned, conducted and most thoroughly analyzed studies reviewed
3 in the last ten years." See FDA Stat. Rev. at 16.

4 Defendants' ex post facto dissection of the HSP fails to
5 undermine its reliability. Scientific studies almost invariably
6 contain flaws. See Federal Judicial Center, Reference Manual on
7 Scientific Evidence 337 (2d ed. 2000) (hereinafter "Ref. Manual")
8 ("It is important to recognize that most studies have flaws.
9 Some flaws are inevitable given the limits of technology and
10 resources.") See also In re Orthopedic Bone Screw Prods. Liab.
11 Litig., MDL No. 1014, 1997 U.S. Dist. LEXIS 6441, at *26-28 (E.D.
12 Pa. May 5, 1997) ("[T]here is no such thing as a perfect epidemi-
13 ological study."; despite weaknesses, court found study suffi-
14 ciently reliable to be admissible) When faced with epidemiolog-
15 ical evidence, the court must determine whether the flaws compro-
16 mise the study's findings. See Ref. Manual at 337.

17 Upon close examination of the arguments and supporting
18 evidence, the court finds the HSP's "flaws" (including any
19 unknown to the FDA and/or NEJM) either inaccurately identified as
20 flaws or inconsequential to the reliability of the study as a
21 whole. The HSP investigators utilized widely accepted and
22 reliable scientific and epidemiological procedures in conducting
23 this study. Because the court finds the methodology scientifi-
24 cally sound, any flaws that might exist go to the weight afforded
25 the HSP, not its admissibility. See Kennedy, 161 F.3d at 1230-31
26 (so long as the court finds the expert's reasoning scientific and

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1 useful to the jury, opposing opinions and evidence go to the
2 weight afforded an expert's opinion, not to admissibility). See
3 also Hemmings v. Tidyman's Inc., 285 F.3d 1174, 1188 (9th Cir.
4 2002) ("[I]n most cases, objections to the inadequacies of a
5 study are more appropriately considered an objection going to the
6 weight of the evidence rather than its admissibility. Vigorous
7 cross-examination of a study's inadequacies allows the jury to
8 appropriately weigh the alleged defects and reduces the possibil-
9 ity of prejudice.") (internal citation omitted), cert. denied,
10 ___ U.S. ___, 123 S.Ct. 854 (2003).

11 The court finds similarly unavailing defendants' arguments
12 as to the significance of the various HSP results and the small
13 numbers upon which they are based. Defendants warn of the
14 consequences of "data fragility," in that small errors or adjust-
15 ments can implicate dramatically different results. Yet, despite
16 the small numbers, the investigators concluded: "Our study
17 provides strong epidemiological evidence of the association
18 between the use of [PPA] and the risk of hemorrhagic stroke."
19 NEJM Article at 1831. Moreover, after conducting three sensitiv-
20 ity analyses because of the "sparse data," the FDA epidemiolo-
21 gists found the association for both appetite suppressants and
22 first use of cough and cold products remained. See FDA Epid.
23 Rev. at 8-9. Because the court finds the methodology reliable,
24 the mere fact that the findings resulted from small numbers does
25 not impact the study's admissibility.

26 That the finding as to cough and cold products reported in

1 the NEJM was not statistically significant by "conventional
2 criteria" also does not detract from the reliability of the
3 study See NEJM Article at 1831 (maintaining that the finding
4 nonetheless "arouse[d] concern regarding safety.") The HSP's one
5 -tailed test looked only to whether PPA increases the hemorrhagic
6 stroke risk, while a two-tailed test also looks to whether an
7 agent protects against the risk. In order to comply with NEJM
8 publication requirements, two-sided results were presented in the
9 published article, altering the p-values and associated confi-
10 dence intervals assigned to the results. Despite this alteration
11 for publication purposes, the HSP final report "demonstrated a
12 statistically significant increased risk of hemorrhagic stroke
13 among both appetite suppressant users and first time users of PPA
14 as a cough/cold remedy." FDA Epid. Rev. at 1-2, 10 (finding the
15 HSP result relating to first use of cough and cold remedies to be
16 as important as the appetite suppressant finding). The court
17 finds that the HSP's one-tailed statistical analysis complies
18 with proper scientific methodology, and concludes that the
19 difference in the expression of the HSP's findings falls far
20 short of impugning the study's reliability. See Ref. Manual at
21 126-27, 358 n.69 ("Since most investigators of toxic substances
22 are only interested in whether the agent increases the incidence
23 of disease (as distinguished from providing protection from the
24 disease), a one-tailed test is often viewed as appropriate."; "a
25 rigid rule [requiring a two-tailed test] is not required if p-
26 values and significance levels are used as clues rather than as

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1 mechanical rules for statistical proof.”)⁹

2 Finally, the HSP investigators and plaintiffs’ witnesses
3 accurately noted the limitations of the previous epidemiological
4 studies on PPA. For example, the Jick study did not consider OTC
5 medication and allowed for a thirty-day interval between the time
6 a patient filled a prescription and suffered a stroke. The court
7 finds that, given these and other limitations, both the Jick and
8 the unpublished O’Neill and Van de Carr study carry little weight
9 in comparison to the HSP. See FDA Stat. Rev. at 5 (“Because of
10 bias involved with the earlier studies, the findings of th[e]
11 carefully planned and conducted [HSP] should be given greater
12 weight as confirmatory safety evidence[.]”)

13 For all of these reasons, the court finds the HSP scientifi-
14 cally reliable evidence upon which to base expert opinion and,
15 therefore, evidence that should not be excluded.

16 b. Non-Epidemiological Lines of Evidence:

17 Plaintiffs’ experts supplement the HSP results with non-
18 epidemiological lines of evidence, including case reports,
19 textbooks and treatises, adverse drug reports, animal studies,
20 and drug analogies. In response, defendants cite to numerous
21

22 ⁹ All parties involved in designing the HSP were interested
23 solely in testing whether PPA increased the risk of stroke. See
24 Dep. of HSP Investigator Ralph Horowitz, Defs.’ Ex. E-7 at 25-27.
25 Cf. Good v. Fluor Daniel Corp., 222 F. Supp. 2d 1236, 1242-43
26 (E.D. Wash. 2002) (finding one-sided method inappropriate where
that analysis assumed the very fact in dispute, that is, whether
there was any exposure to radiation in excess of limits
established by federal regulation).

1 decisions describing the limitations of this non-epidemiological
2 evidence.¹⁰

3 Defendants isolate these sources, rather than considering
4 the whole. Non-epidemiological sources are frequently utilized
5 by experts in rendering scientific opinions and, under Daubert,
6 should be considered by the court in assessing the reliability of
7 those opinions. See, e.g., Kennedy, 161 F.3d at 1228-31 (finding
8 trial court abused its discretion by excluding expert testimony
9 based on, inter alia, peer-reviewed articles, clinical trials and
10 product studies conducted by the manufacturer, and a state health
11 department's review of reported cases of adverse reactions);
12 Hopkins v. Dow Corning Corp., 33 F.3d 1116, 1124-25 (9th Cir.
13 1994) (upholding trial court's admission of expert testimony
14 based on, inter alia, clinical experience and studies, medical
15 literature, and general scientific knowledge about drug's proper-
16 ties established by animal studies and biophysical data).

17 In considering the non-epidemiological evidence relied upon
18 by plaintiffs' experts, the court finds significant the sheer
19

20 ¹⁰ See, e.g., Schudel v. General Electric, 120 F.3d 991, 996-
21 97 (9th Cir. 1997) (noting testimony that small differences in
22 molecular structure of different agents often have significant
23 consequences); Glastetter v. Novartis Pharms. Corp., 252 F.3d
24 986, 989-90 (8th Cir. 2001) (stating that case reports are not
25 scientifically valid proof of causation); Glastetter v. Novartis
26 Pharms. Corp., 107 F. Supp. 2d 1015, 1034 & n.18 (E.D. Mo. 2000)
(finding textbook and treatise conclusions no more reliable than
the case reports on which they were based); Sanderson v. Int'l
Flavors and Fragrances, Inc., 950 F. Supp. 981, 997 (C.D. Cal.
1996) (a party proffering animal studies must provide good
grounds for extrapolating from animals to humans).

1 volume of case reports, case series, and spontaneous reports
2 associating PPA with hemorrhagic stroke in women. See, e.g.,
3 Rider v. Sandoz Pharms. Corp., 295 F.3d 1194, 1202 (11th Cir.
4 2002) (noting that the district court identified the types of
5 evidence that would have been considered reliable, including,
6 inter alia, "a very large number of case reports.") While not
7 conclusive, the multitude of textbooks and treatises including
8 PPA as a risk factor for stroke adds to the reliability of
9 plaintiffs' experts' opinions.¹¹ See Daubert, 509 U.S. at 594
10 ("Widespread acceptance can be an important factor in ruling
11 particular evidence admissible[.]") The non-epidemiological
12 evidence also gains added legitimacy from the fact that several
13 of plaintiffs' experts base their opinions, in part, on independ-
14 ent PPA-related research. See Daubert II, 43 F.3d at 1317.¹²

16 ¹¹ Plaintiffs list over a dozen medical textbooks associating
17 PPA with high blood pressure and stroke. See, e.g., John C.M.
18 Brust, Stroke and Substance Abuse, in Uncommon Causes of Stroke
19 132, 133 (Julian Bogousslavsky & Louis R. Caplan eds., 2001); The
Little Black Book of Neurology 170-72 (Bonner, James S. & Jo
Jaeger Bonner eds. 2d ed., 1991).

20 ¹² Drs. Pentel, Zaloga, and Lake conducted human clinical and
21 animal studies on PPA See also Glaser v. Thompson Med. Co., 32
22 F.3d 969, 972-75 (6th Cir. 1994) (finding scientifically reliable
23 Dr. Zaloga's opinion that PPA-containing Dexatrim can cause
24 severe hypertension). The remaining PSC-identified experts base
25 their opinions on their clinical experience and training, review
26 of the documents and literature, and/or studies and publications
on stroke and other toxic substances. For each, the court has
"plumbed the depths" between their citations and conclusions and
found their opinions sufficiently grounded in the scientific
method. See Metabolife Intern., Inc. v. Wornick, 264 F.3d 832,
845 (9th Cir. 2001).

1 Taking into consideration all of the lines of evidence upon
2 which plaintiffs' experts rely, including the HSP, expert opin-
3 ions associating PPA with hemorrhagic stroke in women above the
4 age of eighteen and below the age of forty-nine clearly satisfy
5 Daubert's reliability prong.¹³

6 c. Recent Article on Aneurysmal SAH:

7 During the final day of the Daubert proceedings, defendants
8 raised challenges relating to a new article by the HSP investiga-
9 tors to be published in the June 2003 issue of the journal
10 "Stroke." See Joseph P. Broderick et al., Major Risk Factors for
11 Aneurysmal Subarachnoid Hemorrhage in the Young are Modifiable,
12 Stroke (2003) (hereinafter "Stroke Article"). Defendants assert
13 that this article demonstrates the lack of an association between
14 PPA and SAHs resulting from the rupture of an aneurysm
15 ("aneurysmal SAH"). The court finds that defendants distort and
16 misinterpret the Stroke Article.

17 The HSP investigators structured the HSP to study hemor-
18 rhagic stroke as a single entity. They did not collect enough
19 data or enroll enough subjects to study PPA in relation to SAH or
20 ICH, let alone a particular type of SAH or ICH.¹⁴ In the Stroke

21
22 ¹³ The court does not find discussion of the so-called
23 "Bradford Hill" criteria, sometimes utilized by scientists in
24 considering questions of causation, necessary or helpful.

25 ¹⁴ All entities involved in designing the HSP approved the
26 joint consideration of ICH and SAH in approving the design of the
study. Moreover, both scientific literature and other studies,
including the Jick study, support consideration of hemorrhagic
stroke as a single entity.

1 Article, the HSP investigators look at the HSP data to identify
2 general risk factors for aneurysmal SAH - a subset of a subset of
3 hemorrhagic stroke. They do not proffer a new epidemiological
4 study on PPA and aneurysmal SAH. Instead, they include in a
5 table, without any corresponding substantive discussion, an odds
6 ratio (1.15) and p-value (0.87) for PPA in relation to aneurysmal
7 stroke.

8 Contrary to defendants' assertion, the PPA odds ratio
9 reported in the Stroke Article, standing alone, is not inconsis-
10 tent with the results of the HSP. The article reports a single
11 PPA index for "any use" of PPA. The resulting 1.15 odds ratio
12 does not differ significantly from the HSP's 1.49 odds ratio for
13 any use of PPA. The article does not look at "first use" of PPA
14 or PPA use in connection with appetite suppression - the two most
15 significant findings of the HSP (3.13 and 16.58 odds ratios
16 respectively) and the two findings upon which plaintiffs' experts
17 primarily based their opinions.

18 Nor does the associated p-value identified for any use of
19 PPA demonstrate the lack of an association. Defendants point to
20 the 0.87 p-value as indicating that the difference between the
21 1.15 odds ratio and the 1.00 null hypothesis value (i.e., no true
22 association between PPA and stroke) is attributable to chance
23 alone. However, plaintiffs' expert, Dr. Kenneth Rothman, ex-
24 plained that a p-value cannot provide evidence of lack of an
25 effect. See Rothman Aff., ¶ 7; Kenneth J. Rothman, Epidemiology,
26 An Introduction at 117 (Oxford Univ. Press 2002). Dr. Rothman

1 clarified that statistical reassurance as to lack of an effect
2 would require an upper bound of a reasonable confidence interval
3 close to the null value. See Rothman Aff., ¶ 7. Calculating a
4 95% confidence interval with a lower bound of 0.5 and an upper
5 bound of 2.6, Dr. Rothman concluded that the data does not
6 provide reassurance about the absence of an association. Id. at
7 ¶ 8.

8 For all of these reasons, the court finds nothing in the
9 Stroke Article undermining the admissibility of plaintiffs'
10 expert opinions associating PPA with aneurysmal SAH.¹⁵

11 3. Hemorrhagic Stroke in the Various "Sub-Populations":

12 The HSP focused on men and women between the ages of eigh-
13 teen and forty-nine. It did not offer any conclusions as to
14 individuals outside of that age range, and the results were
15 inconclusive as to men. The lack of epidemiological evidence
16 directly associated with men, children, and individuals above the
17 age of forty-nine is not fatal under Daubert. See, e.g., Ken-
18

19 ¹⁵The court also finds defendants' purported surprise at
20 their May 2003 discovery of the Stroke Article disingenuous.
21 Defendants fail to mention that several of their experts were
22 present for a February 2003 American Stroke Association meeting
23 at which the abstract for the article and the data were
24 presented. See Feldmann Aff., ¶ 3. The court similarly rejects
25 defendants' accusation that Dr. Feldmann denied knowledge of the
26 analysis underlying the Stroke Article in his November 2002
deposition. A full reading of Dr. Feldmann's testimony exposes
no such subterfuge. Given that defendants have since extensively
questioned Dr. Feldmann under oath about the article, and given
the above-described conclusion as to the article's lack of
significance, the court denies defendants' request for additional
discovery on this subject.

1 nedey, 161 F.3d at 1229-30. See also In re Berg Litig., 293 F.3d
2 1127, 1130 (9th Cir. 2002). As discussed below, plaintiffs'
3 experts demonstrate that it is scientifically acceptable to
4 extrapolate the conclusions of the HSP to these sub-populations.

5 a. Hemorrhagic stroke in individuals above the age of
6 forty-nine:

7 Defendants generally dispute whether extrapolation to a
8 different age group is good science. However, in arguing against
9 extrapolation to individuals above the age of forty-nine, defen-
10 dants' experts primarily point to the fact that the risk of
11 stroke increases as age increases. The court sees no reason why
12 the increasing risk of stroke would render the HSP and the non-
13 epidemiological lines of evidence unreliable as applied to this
14 age group. See Dep. of Dr. Jerome Avorn, Defs.' Ex. E-1 at 363
15 ("[A]ll of the evidence we have is that risks only go up in the
16 elderly. . . . [T]here are no drugs I'm aware of that get safer
17 the older you get.") As such, the court finds testimony associ-
18 ating PPA with hemorrhagic stroke in individuals above the age of
19 forty-nine reliable and, thus, admissible under Daubert.

20 b. Hemorrhagic stroke in children and men:

21 Defendants accurately note that, in addition to the absence
22 of supportive epidemiological evidence, plaintiffs rely on a
23 smaller number of case reports directly relating to children and
24 men. Also, in disputing the propriety of extrapolating evidence
25 from women to men, and from adults to children, defendants and
26 their experts go to great lengths to highlight differences

1 between these sub-populations.

2 Plaintiffs' experts assert that the weight of the evidence,
3 including that obtained through extrapolation, supports the
4 opinion that PPA can cause stroke in children and men.¹⁶ The
5 court must address whether this extrapolation constitutes good
6 science See, e.g., Domingo, 289 F.3d at 606 ("[S]tudies involv-
7 ing similar but not identical situations may be helpful, [so long
8 as] an expert [] set[s] forth the steps used to reach the conclu-
9 sion that the research is applicable.")

10 It is axiomatic that children differ from adults in various
11 ways, just as younger children differ from older children, and
12 younger adults differ from the elderly. Men and women, likewise,
13 differ in some respects. As might be expected, the incidence
14 rates of stroke, types of stroke, and some of the risk factors
15 for stroke vary between these groups. Plaintiffs' experts
16 concede these differences, but maintain that these sub-popula-
17 tions share far more similarities than differences. After
18 considering all possible differences, plaintiffs' experts find no
19 basis for concluding that PPA poses a risk exclusive to adult
20 females.¹⁷

21
22 ¹⁶ In proffering evidence directly relevant to these sub-
23 populations, plaintiffs point to most of the same non-
24 epidemiological types of evidence discussed above, including,
inter alia, case reports, textbooks and other medical literature,
and biological plausibility arguments

25 ¹⁷ Similarly, the FDA did not differentiate between men and
26 women, and found no reason to believe the risks posed by PPA were
limited to individuals within the age range studied in the HSP.

1 Because of the many barriers to including children in
2 studies, scientists and medical practitioners routinely extrapo-
3 late study results and data on adults to children. This prac-
4 tice, despite its limitations, finds wide support in reputable
5 sources. See, e.g., Robert M. Ward, *Adverse Effects of Drugs in*
6 *the Newborn, in Rudolph's Pediatrics* 146 (Colin D. Rudolph et al.
7 eds. 21st ed., 2001) ("Children continue to be excluded from
8 studies of most new drugs, so that drug therapy of those patients
9 is seldom guided by large controlled trials."); George C.
10 Rodgers, Jr. & Nancy J. Matyunas, *Oski's Pediatrics* 61-62 (Julia
11 A. McMillan et al. eds. 3d ed., 1999) ("In the absence of con-
12 trolled, randomized clinical trials in children, pediatricians
13 must either extrapolate information from adult studies or use
14 uncontrolled reports of clinical experience in children, both of
15 which have major flaws.")¹⁸ Plaintiffs' experts also point to
16 the presumption in pediatric toxicology that toxic effects seen
17 in adults will be as great, if not greater, in children. See
18 Michael J. Rieder, *Adverse Drug Reactions in Neonates, Infants,*

19 _____
20 See FDA Proposal to Withdraw Approval of New Drug Applications,
21 66 Fed. Reg. 42670 (proposed Aug. 14, 2000) ("Although the Yale
22 study focused on men and women 18 to 49 years of age, the agency
has no reason to believe that the increased risk of hemorrhagic
stroke is limited to this population.")

23 ¹⁸See also Gabrielle de Veber, *Cerebrovascular Disease in*
24 *Children, in 2 Pediatric Neurology, Principles & Practice* 1099
25 (Kenneth F. Swaiman & Stephen Ashwal eds. 3d ed., 2000) ("[T]here
26 has been no research studying medical therapy for childhood
stroke. Current treatments are therefore, of necessity, based on
therapies proven in adult stroke patients with biologic plausi-
bility and safety data in pediatric patients when available.")

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1 Children, and Adolescents, in Problems in Pediatric Drug Therapy
2 285 (Louis A. Pagliaro & Ann Marie Pagliaro eds. 4th ed., 2002)
3 ("Neonates, infants, and young children are at substantially
4 increased risk for [adverse drug reactions], primarily because of
5 their immature drug elimination organ function, but also due to
6 differences in other pharmacokinetic factors (i.e. volume of
7 distribution).")

8 Plaintiffs' experts attest to the equally commonplace
9 practice of extrapolation between the genders, based on, in
10 significant part, the historical exclusion of women from scien-
11 tific studies. Defendants' experts note current studies account-
12 ing for the differences between men and women, but do not estab-
13 lish that this very recent shift has yet effectuated a change in
14 the practice of extrapolation. See Daubert Hearing Record (Apr.
15 28-30, 2003) at 427-30 (hereinafter "Record"). Until such a
16 change occurs, the court will not deem this practice scientifi-
17 cally unreliable. See Rider, 295 F.3d at 1202 ("Given time,
18 information, and resources, courts may only admit the state of
19 science as it is.")¹⁹

20 Plaintiffs' experts clearly set forth the steps followed in
21 extrapolating this evidence. See Domingo, 289 F.3d at 606.

22 _____
23 ¹⁹Additionally, plaintiffs' experts do not dispute that
24 women may be at a greater risk from PPA than men, and stress
25 that, in either gender, strokes are an "uncommon adverse
26 risk. See Record at 132-33, 207-08, 297. They maintain the need
for extrapolation given the unsurprisingly smaller amount of
evidence directly relating to the male outliers.

1 While defendants demonstrate some of the problems posed by
2 extrapolation and dispute the conclusions reached, they do not
3 establish that plaintiffs' experts utilized scientifically
4 unreliable methodologies. See Kennedy, 161 F.3d at 1230-31
5 (noting that defendant failed to introduce any evidence that
6 expert's reasoning was not scientifically valid). The court
7 finds the direct and extrapolated evidence sufficiently reliable
8 evidence upon which to base expert opinion. As such, it also
9 finds opinions as to these sub-populations admissible under
10 Daubert.

11 4. Ischemic Stroke:

12 Ischemic stroke results from the blocking of blood flow in a
13 cerebral vessel, depriving brain tissue beyond the blockage of
14 oxygen. The vast majority of strokes are ischemic.

15 Defendants assert that plaintiffs lack scientific evidence
16 and general acceptance in the medical community as to a causative
17 relationship between PPA and ischemic stroke. Plaintiffs'
18 experts, represented by Dr. Steven Levine at the Daubert hearing,
19 opine that PPA, on rare occasions and in some people, can trigger
20 an ischemic stroke.

21 Dr. Levine's opinion rests on case and adverse drug reports,
22 biological plausibility, comparison to other sympathomimetics and
23 naturally occurring conditions with altered sympathetic tone, PPA
24 blood pressure studies, textbook and other references, and both
25 his own and others' clinical experience. As noted above, the
26 lack of epidemiological evidence does not render expert opinions

1 on this issue unreliable. See, e.g., Kennedy, 161 F.3d at 1229-
2 30. However, in comparison to hemorrhagic stroke, plaintiffs'
3 experts on ischemic stroke unquestionably rely on a smaller
4 volume of evidence directly relating to PPA. For example, while
5 numerous textbooks and treatises associate PPA with ischemic
6 stroke, only a few published case reports and only some twenty-
7 five percent of the stroke cases in the FDA SRS database involved
8 ischemic injuries associated with PPA. As such, the court finds
9 a more detailed analysis of the expert testimony and various
10 lines of evidence appropriate.

11 Dr. Levine testified as to scientific cause and effect
12 between PPA and ischemic stroke, looking to biological plausibil-
13 ity, temporal association, and dose response. He found temporal
14 association demonstrated by the case and adverse drug reports,
15 clinical experience, and textbooks, and pointed to evidence
16 establishing that higher doses of PPA were more likely to cause
17 an adverse response. In addressing biological plausibility, Dr.
18 Levine identified the very same mechanisms postulated as triggers
19 for PPA-induced hemorrhagic stroke, including an acute rise in
20 blood pressure, vasoconstriction or vasospasm, and, in some
21 cases, vasculitis. He maintained that an acute PPA-induced blood
22 pressure increase can in some individuals disrupt the brain's
23 autoregulation process, causing reactive vasoconstriction in
24 blood vessels and leading to an ischemic stroke. He illustrates
25 PPA's vasoconstrictive effect in its role as a nasal mucosa
26 vasoconstrictor, constricting blood vessels and reducing blood

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1 flow in order to treat nasal symptoms.

2 Dr. Levine supplements this theory by comparing PPA to other
3 sympathomimetics, including amphetamine, cocaine, and ephedrine.
4 He maintains that these agents share similar chemical structure,
5 function, and effects, and can cause both ischemic and hemor-
6 rhagic stroke. Dr. Levine points to scientific literature and
7 animal studies indicating that these other sympathomimetics both
8 increase blood pressure and induce vasoconstriction,²⁰ and
9 epidemiologic data demonstrating an ischemic stroke association
10 to both amphetamines and cocaine. Plaintiffs also point to the
11 American Heart Association's recent recommendation that ephedrine
12 - which, according to Dr. Levine, has a lesser vasoconstrictive
13 action than PPA - be removed from the market given its adverse
14 cardiovascular effects.²¹

15
16 ²⁰ See, e.g., Harold P. Adams, Jr. et al., Ischemic
17 Cerebrovascular Disease 295-96 (2001) (the most commonly
18 implicated drugs with respect to ischemic stroke, cocaine and
19 amphetamines, are "both potent vasoconstrictors that lead to
20 increased blood pressure"; "Narrowing (vasoconstriction) of the
21 intracranial arteries has been found in persons with ischemic
22 stroke following abuse of cocaine or methamphetamines.")

23 ²¹ See American Heart Association Urges Ban on Ephedra-based
24 Supplements, at <http://www.americanheart.org> (May 14, 2003) ("The
25 side-effects associated with [OTC ephedra-based dietary
26 supplements] are primarily cardiovascular-related. A review of
FDA data on reported events indicated high blood pressure,
stroke, heart attacks and death linked to ephedra use. The
American Heart Association believes that these reported events
are the tip of the iceberg.") As noted, Dr. Levine also
analogizes the effect of PPA to naturally occurring conditions
with altered sympathetic tone, describing eclamptic and pre-
eclamptic women suffering episodes of cerebral vasoconstriction
and vasospasm resulting in ischemic and hemorrhagic stroke.

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1 The fact that the mechanism remains unclear does not call
2 the reliability of the opinion into question: "Not knowing the
3 mechanism whereby a particular agent causes a particular effect
4 is not always fatal to a plaintiff's claim. Causation can be
5 proved even when we don't know precisely *how* the damage occurred,
6 if there is sufficiently compelling proof that the agent must
7 have caused the damage *somehow*." Daubert II, 43 F.3d at 1314.
8 See also Daubert, 509 U.S. at 590 ("Of course, it would be
9 unreasonable to conclude that the subject of scientific testimony
10 must be 'known' to a certainty; arguably, there are no certain-
11 ties in science.")

12 Plaintiffs bolster their theory on the mechanism behind PPA-
13 induced ischemic stroke. The above-described human clinical
14 trials and animal studies demonstrate PPA's effect on blood
15 pressure. PPA's vasoconstrictive effect and ischemic stroke
16 association finds support in scientific literature. See, e.g.,
17 Rashmi Kothari & William G. Barsan, Stroke, in Rosen's Emergency
18 Medicine: Concepts and Clinical Practice at 1435 (John A. Marx et
19 al. eds. 5th ed., 2002) ("Recreational drugs such as cocaine,
20 [PPA], and amphetamines are potent vasoconstrictors associated
21 with both ischemic and hemorrhagic stroke."); Harold P. Adams,
22 Jr. et al., Ischemic Cerebrovascular Disease 297 (2001) (naming
23 PPA as a medication with vasoconstrictive properties implicated
24 as leading to stroke); Michael A. Sloan, Toxicity/Substance
25 Abuse, in Primer on Cerebrovascular Diseases at 413 (K.M.A. Welch
26 et al. eds., 1997) (associating PPA with vasospasm and beading).

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1 See also Record at 631, 637-38 (although denying that PPA causes
2 vasospasm, defense expert Dr. Brian Hoffman conceded PPA's
3 vasoconstrictive effect).

4 Scientific literature also supports the practice of compar-
5 ing PPA to other sympathomimetics. See, e.g., John C.M. Brust,
6 Stroke and Substance Abuse, in Uncommon Causes of Stroke 133
7 (Julian Bogousslavsky & Louis R. Caplan eds., 2001) (describing
8 PPA as an "amphetamine-like drug" and one of a group of psycho-
9 stimulants with "well-recognized" ischemic or hemorrhagic stroke
10 complications). Dr. Levine outlined the steps he utilized in
11 applying evidence and research relating to these other agents to
12 PPA. See Domingo, 289 F.3d at 606-07.²² Just as with extrapola-
13 tion between the sub-populations, defendants identify some of the
14 problems in comparing PPA with other sympathomimetics. However,
15 again, they do not demonstrate that this practice fails to accord
16 with acceptable methods and procedures of science. See Kennedy,

20 ²²The court finds the Ninth Circuit cases excluding
21 testimony relying on "similar but not identical" studies and
22 evidence distinguishable. See, e.g., Domingo, 289 F.3d at 606-07
23 (expert's theory had never been published, and expert did not set
24 forth the steps utilized in reaching a conclusion based on animal
25 studies or point to studies supporting every necessary link in
26 the theory of causation); Schudel, 120 F.3d at 997 (court found
"no showing that necessary extrapolation [from studies involving
either different agents or different types of exposure] was
scientifically acceptable."); see also Rider, 295 F.3d at 1202
(expert relied on evidence that agent could cause ischemic stroke
to prove it could cause hemorrhagic stroke).

1 161 F.3d at 1230.²³

2 The expert opinions offered on the PPA/ischemic stroke
3 association rest on more than simply the "ipse dixit" of the
4 experts. Joiner, 522 U.S. at 146. In addition to the evidence
5 proffered as to biological plausibility and through comparison to
6 like agents, plaintiffs' experts rely on case and adverse drug
7 reports, textbooks and treatises, and the clinical experience of
8 several experts and other scientists. The court again finds that
9 the cumulative effect of this evidence satisfies the mandate of
10 Daubert. See, e.g., Kennedy, 161 F.3d at 1228-31; Hopkins, 33
11 F.3d at 1124-25 (finding expert testimony relying on, inter alia,
12 clinical experience and studies, medical literature, and general
13 scientific knowledge about a drug's properties based "on the
14 types of scientific data and utiliz[ing] the types of scientific
15 techniques relied upon by medical experts in making determina-

16
17 ²³ Upon being asked what inferences were permissible in
18 considering scientific evidence, defense expert Dr. Gregory
19 Albers testified that, in the absence of high quality data,
20 inferences could be made by looking to "biological plausibility,
21 temporal associations, [and] wealth of anecdotal data." Record
22 at 589. Dr. Levine followed this precise formula. Dr. Albers
23 also agreed that there was "quite a bit of suspicion" as to the
24 association between ischemic stroke and cocaine/amphetamines, and
25 noted that he performed drug screens on his ischemic stroke
26 patients Id. at 594-96. Additionally, in arguing against
general acceptance, Dr. Albers pointed to a "strong scientific
statement[,] " put out by the "very discerning" American Heart
Association ("AHA"), not mentioning PPA as a risk factor for
ischemic stroke. Id. at 581. He later opined that ephedrine,
also not included in the aforementioned statement, has not been a
well-accepted cause of ischemic stroke, just prior to learning
that the AHA recently recommended its removal from the market.
Id. at 584-85.

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1 tions regarding toxic causation where there is no solid body of
2 epidemiological data to review.") See also Glaser v. Thompson
3 Med. Co., 32 F.3d 969, 972-75 (6th Cir. 1994) (finding scientific-
4 cally reliable Dr. Zaloga's opinion that PPA-containing Dexatrim
5 can cause severe hypertension, based on five of his own published
6 studies, the published articles of other medical researchers,
7 case reports, and his own clinical experience.")²⁴

8 Admittedly, the purported PPA-ischemic stroke association
9 poses a far more difficult question under Daubert than that
10 presented by hemorrhagic stroke. Indeed, while Dr. Levine found
11 "grade B" evidence for causality between PPA and hemorrhagic
12 stroke, the evidence associating PPA with ischemic stroke, just
13 as with hemorrhagic stroke in children and men, fell somewhere
14

15 ²⁴Contrary to defendants' assertion, the court finds nothing
16 in the Glaser decision incompatible with the Daubert trilogy of
17 cases. Defendants also point to circuit court decisions
18 affirming exclusion of expert testimony relating to the drug
19 "Parlodel." See Rider, 295 F.3d 1194 (11th Cir. 2002); Hollander
20 v. Sandoz Pharms. Corp., 289 F.3d 1193 (10th Cir. 2002);
21 Glastetter, 252 F.3d 986 (8th Cir. 2001). These decisions are
22 not binding on this court and involved an entirely different
23 drug. Moreover, no circuit court has yet reviewed any of the
24 several different district court decisions finding Parlodel
25 causation evidence scientifically reliable. As stated by the
26 Tenth Circuit in Hollander: "[W]hen coupled with th[e]
deferential [abuse of discretion] standard of review, Daubert's
effort to safeguard the reliability of science in the courtroom
may produce a counter-intuitive effect: different courts relying
on the essentially the [sic] same science may reach different
results." 289 F.3d at 1206-07 (citing Ref. Manual at 27 and
Brasher v. Sandoz Pharms. Corp., 160 F. Supp. 2d 1291, 1299 n.17
(N.D. Ala. 2001) (observing that the Eighth Circuit's decision in
Glastetter "does not necessarily [establish] that an inconsistent
holding by this court would constitute an abuse of discretion."))

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1 below a "grade C," with "associated grade B" evidence from the
2 class of like agents.

3 However, the court need not determine the accuracy of
4 plaintiffs' experts' conclusions. As stated by the Ninth Cir-
5 cuit:

6 Judges in jury trials should not exclude expert testi-
7 mony simply because they disagree with the conclusions
8 of the expert. The *Daubert* duty is to judge the rea-
9 soning used in forming an expert conclusion. The test
10 is whether or not the reasoning is scientific and will
11 assist the jury. If it satisfies these two require-
12 ments, then it is a matter for the finder of fact to
13 decide what weight to accord the expert's testimony.
In arriving at a conclusion, the factfinder may be
confronted with opposing experts, additional tests,
experiments, and publications, all of which may in-
crease or lessen the value of the expert's testimony.
But their presence should not preclude the admission of
the expert's testimony - they go to the *weight*, not the
admissibility.

14 Kennedy, 161 F.3d at 1230-31. See also Daubert, 509 U.S. at 596
15 ("Vigorous cross-examination, presentation of contrary evidence,
16 and careful instruction on the burden of proof are the tradi-
17 tional and appropriate means of attacking shaky but admissible
18 evidence.") (citing Rock v. Arkansas, 483 U.S. 44, 61 (1987)).
19 Here, for the reasons described above, the court finds that
20 plaintiffs' experts employed good science in reaching their
21 conclusions. As such, the court finds plaintiffs' expert opin-
22 ions on ischemic stroke admissible under Daubert.

23 5. Cardiac Injuries:

24 Plaintiffs also posit a causal relationship between PPA and
25 cardiac injuries. The myocardial injuries identified include
26 myocardial ischemia (angina; insufficient blood flow to heart

1 muscle tissue), myocardial infarction (heart attack), myocardial
2 necrosis (destruction of heart muscle cells), myocarditis (in-
3 flammation of heart muscle walls), and cardiomyopathy (primary
4 heart muscle mass disease). Plaintiffs also implicate some
5 twelve different types of cardiac arrhythmias, including ventric-
6 ular tachycardia (accelerated ventricular rhythm), ventricular
7 fibrillation (contraction of ventricle), and bradyarrhythmia
8 (deceleration of heart's rhythm).

9 Plaintiffs' expert, Dr. Irvin Goldenberg, attested to the
10 relationship between PPA and cardiac injuries at the Daubert
11 hearing. Lacking epidemiological evidence, Dr. Goldenberg drew
12 upon animal studies, human clinical trials, case reports, clini-
13 cal experience, comparison to other sympathomimetics, and text-
14 book references. He testified as to, inter alia, biological
15 plausibility, temporal association, and dose response. Thus, at
16 first glance, Dr. Goldenberg's methodology mirrors that employed
17 by Dr. Levine. However, upon closer analysis, the court finds
18 critical distinctions between these expert opinions.

19 Applied across the broad spectrum of cardiac injuries, the
20 evidence proffered by Dr. Goldenberg spreads far too thin to
21 reliably support expert scientific testimony. See Joiner, 522
22 U.S. at 146 (court may conclude that there is simply too great an
23 analytical gap between the data and the opinion proffered). For
24 example, most of the myocardial injury case reports involved what
25 Dr. Goldenberg referred to as "small heart attacks," while the
26 textbooks he identified associate PPA with cardiomyopathy and

1 coronary artery disease. See Daubert Hearing Record (May 29,
2 2003) at 38-40, 43-44 (hereinafter "Record II"). The arrhythmia
3 case reports similarly do not represent a preponderance of any
4 particular type(s) of arrhythmia. The remaining lines of evi-
5 dence, including several animal studies, human clinical trials,
6 three cases recalled from Dr. Goldenberg's clinical experience,
7 and a comparison to like agents, do not otherwise account for the
8 breadth of injuries at issue.²⁵

9 The evidence also fails to account for the incredible
10 variety of proposed mechanisms. In comparison to the consistent
11 explanations of proposed mechanisms for hemorrhagic and ischemic
12 stroke, Dr. Goldenberg identified, by defendants' count, some
13 thirty-five different biological mechanisms for the association
14 between PPA and the various cardiac injuries. Dr. Goldenberg did
15 not proffer support for his opinions as to the bulk of these
16 mechanisms.

17 To the contrary, Dr. Goldenberg's primary explanation relied
18 on PPA's vasoconstrictive effect. However, defendants' expert,
19 Dr. Thomas Michel, testified that PPA's vasoconstrictive effect
20 on coronary arteries was extremely limited. Id. at 84-86; 90-92.
21 Dr. Michel testified that PPA's primary mechanism of action was
22

23 ²⁵ The court is mindful of the fact that strokes may be
24 broken down into numerous categories and sub-categories.
25 However, in contrast to the experts on stroke, Dr. Goldenberg
26 failed to provide comprehensive support for the various cardiac
injuries or to demonstrate the propriety of considering cardiac
injuries as a whole in relation to PPA.

1 its stimulation of alpha adrenergic receptors, resulting in PPA
2 binding to those receptors and eliciting vasoconstriction.
3 Because of the notably lower density of alpha receptors in
4 coronary arteries, PPA was less likely to cause vasoconstriction
5 in coronary arteries than in other vascular beds. This testimony
6 calls into question Dr. Goldenberg's opinion on the proposed
7 vasoconstrictive mechanism for cardiac injuries attributed to
8 PPA. Yet, neither Dr. Goldenberg, nor plaintiffs' counsel
9 addressed this distinction during the Daubert hearing.²⁶

10 Finally, deficiencies in the assorted lines of evidence
11 further exacerbate the gap between Dr. Goldenberg's opinion and
12 the evidence relied upon. For instance, while Dr. Goldenberg
13 testified as to severe cardiac injuries stemming from PPA con-
14 sumption, the case reports showed, in general, no long term
15 adverse effects associated with PPA. See Record II at 36 (Dr.
16 Goldenberg testified: "[A]ll these [myocardial injury] cases I'm
17 going to tell you, they took the drug, they came in within a
18 couple hours afterwards[.] When the drug was withdrawn, they had
19 no problems that we know of.") and 60-62 (defendants' expert
20

21 ²⁶ Plaintiffs later pointed to a single textbook only
22 indirectly supporting their assertion that coronary arterial beds
23 are as responsive to PPA's vasoconstrictive effect as cerebral
24 arteries. See Brian B. Hoffman, Catecholamines, Sympathomimetic
25 Drugs, and Adrenergic Receptor Antagonists, in Goodman &
26 Gilman's: The Pharmacological Basis of Therapeutics at 222, table
10-2 (McGraw-Hill 10th ed., 2001) (showing that norepinephrine,
which plaintiffs maintain PPA releases from nerve terminals as an
indirect effect, has a greater effect on coronary blood flow than
it does on cerebral blood flow).

1 testified that seven out of twenty arrhythmia case report pa-
2 tients spontaneously recovered without any treatment, while seven
3 others recovered completely with treatment). Similarly, while
4 Dr. Goldenberg presented testimony as to individuals consuming
5 human therapeutic doses of PPA, three of the animal studies found
6 no pathology at doses significantly beyond human therapeutic
7 dose, including doses 1000 and 235 times that level. Id. at 75-
8 76, 83-84. Also, beyond offering a few isolated examples, Dr.
9 Goldenberg only alluded to the existence of numerous textbooks
10 and treatises supporting his opinion.

11 Dr Goldenberg's scattershot expert testimony lacks both the
12 cumulative evidentiary support and the thoroughness the court
13 found reliable with respect to both hemorrhagic and ischemic
14 stroke. Simply put, the evidence proffered by Dr. Goldenberg
15 fails to reliably support his ultimate opinion. See Joiner, 522
16 U.S. at 146. As such, the court finds expert opinions as to a
17 relationship between PPA and cardiac injuries inadmissible under
18 Daubert.

19 IV. CONCLUSION

20 For the reasons described above, the court GRANTS in part
21 and DENIES in part defendants' motion to preclude plaintiffs'
22 expert opinions as to general causation. The court finds expert
23 testimony as to an association between PPA and hemorrhagic or
24 ischemic stroke, in either gender and any age group, admissible.
25 The court finds expert testimony associated with seizures,
26 psychoses, injuries occurring more than three days after inges-

1 tion of a PPA-containing product, and cardiac injuries inadmissi-
2 ble.

3 DATED at Seattle, Washington this 18th day of June, 2003.

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5 BARBARA JACOBS ROTHSTEIN
6 UNITED STATES DISTRICT JUDGE
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