Not Reported in A.2d, 2003 WL 22417238 (N.J.Super.L.)

Superior Court of New Jersey, Law Division.
In re: PHENYLPROPANOLAMINE (PPA)
July 21, 2003.

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OPINION

CORODEMUS, J.

On the Brief

*1 Presently before the court is the Phenylpropanolamine ("PPA") defendants' motion to exclude or limit the expert testimony of Jerome Avron, M.D., Rubin Bressler, M.D.,

Richard W. Clapp, D.Sc., Robert A. Egan, M.D., Edward Feldmann, M.D., Steven J. Kittner, M.D., Raymond C. Lake, M.D., Ph.D., James R. McDowell, M.D., Walter Molofsky, M.D., Paul R. Pentel, M.D., Steven W. Pray, Ph.D., George Ricaurte, M.D., William E. Shell, M.D., Stanley Tuhrim, M.D., Alan Woolf, M.D., M.P.H., Gary P. Zaloga, M.D., Steven R. Levine, M.D., and Paul Wax, M.D. pursuant to New Jersey Rules of Evidence 702 and 703 and the respective responses thereto. Plaintiffs' opposition is predicated on the New Jersey Supreme Court's recent decision of *Kemp v. State of New Jersey*, 174 N.J. 412, 809 A.2d 77 (2002). For the reasons set forth below, the court will grant in part and deny in part the motion to exclude expert testimony.

I. INTRODUCTION

Plaintiffs have designated sixteen individuals as their generic experts for civil actions centralized in New Jersey state courts as a mass tort, under case code 264.[FN1] The primary issue at trial is whether ingestion of PPA caused consumers stroke. In support of plaintiffs' affirmative answer they offer expert testimony that allegedly addresses general causation, by seeking to testify about the link between ingestion of PPA products and being at an increased risk of stroke. Plaintiffs also offer testimony regarding labeling in mainly over-the-counter ("OTC") medication. PPA was found in many well known over the counter products such as: Acutrim, Dexatrim, Alka-Seltzer, Comtrex, Contact, Coricidin, Dimetapp, Naldan-DX, Robitussin CF, Tavist-D, and Triamenic.

FN1. Defendants move to preclude expert opinions from 18 experts. However, Plaintiffs have only designated 16 experts in the New Jersey PPA litigation. The remaining two experts, Drs. Bressler and Shell have only been designated in the federal multi-district litigation and, as a result, the court will not consider the admissibility of either Dr. Bressler or Dr. Shell unless a party designates one of these individuals as an expert.

The parties had agreed as memorialized in Case Management Order No. 7, entered on January 16, 2003, to submit *omnibus* motions on behalf of all defendants with an *omnibus* opposition by plaintiffs. Additionally, the parties agreed to participate in a video/digitalized recordation of all *Kemp* hearings with CD-ROMs, hearing transcript, and their respective briefs as to Drs. Levine, Wax, and Pray, "or any generic expert(s) designated in the MDL including but not limited to, MDL experts on general causation and the name(s) of the MDL experts upon whose opinion(s) each Plaintiff intends to rely." Case Management Order No. 7 pg. 1 (January 16, 2003). Other than Drs. Levine, Wax, and Pray, and the MDL experts whom Plaintiffs may identify as set forth above, no Plaintiff is permitted to designate any other generic expert to offer an expert opinion under paragraph 1 of the January 16, 2003 consent order in this matter. *Id.* Accordingly, this court reviewed videos, briefs, and transcripts of *Kemp* hearings for Drs. Levine, Wax, and Pray.

Subsequent to the above mentioned *Kemp* hearings, *Daubert* [FN2] hearings were conducted in the federal multi-district litigation before the Honorable Barbara Rothstein, United States District Court, Western District of Washington at Seattle, MDL No. 1407. In attendance were several state court judges from the western United States, with New Jersey, Pennsylvania, and New York jurists invited via live videoconferencing between Seattle, Washington and New Brunswick, New Jersey. This procedure of cooperative federal/state shared discovery is specifically endorsed by the National Judicial Center. *See* MANUAL FOR COMPLEX LITIGATION, § 33.23 (3 ed.1995). This court incorporates the testimony, transcript, arguments, and briefs from the United States District Court for the Western District of Washington to the extent they apply to experts offered by Plaintiffs in New Jersey and become issues in those cases.

FN2. *See* *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 *U.S.* 579, 113 *S.Ct.* 2786, 125 *L.Ed* 2d 469 (1993)(articulating standards for the admissibility of scientific evidence).

*2 This court's objective in deciding the *Kemp* motions are: (1) delineate the scope of the court's rulings by discussing certain categories of challenges to these witnesses' testimony that, in the court's opinion, do not implicate New Jersey Rules of Evidence 702 and 703 or *Kemp*, or have already been addressed by the court in prior rulings; (2) set out the standards for admissibility of expert testimony; and finally (3) address the specific *Kemp* challenges to the testimony for each witness and the court's rulings thereon. For such undertaking, it is necessary to begin with an understanding of PPA and its historical place in the commercial market.

II. BACKGROUND

A. History of PPA

Originally, PPA was synthesized as an alternative to ephedrine for the maintenance of blood pressure. J.P. Morgan et al., *Phenylpropanolamine: Risks, Benefits, and Controversies*, 11-24 (Praeger Publishers 1985). Beginning in the late 1930s, PPA was marketed and widely used in prescription and non-prescription cough-cold products. By the late 1970s, PPA began to be marketed and widely used in appetite suppressants. *Id.* Billions of doses of PPA have been sold.

Despite the pervasive use of PPA, the Food and Drug Administration ("FDA") never ruled that PPA was safe. *See* 59 Fed.Reg. 43,386 (1994) Because PPA was in commercial use before the adoption of existing FDA rules and procedures governing the sale of OTC drugs, PPA was not subjected to a full safety and efficacy analysis prior to marketing. Instead, the FDA subjected PPA to its monograph review process in 1972. The OTC monograph review consists of a three-phase rule-making process: classification, acceptance of the proposal by the FDA, and adoption of the classification following public comment. There are three categories of classification. Category I means generally recognized as safe and effective. Category II means not generally recognized as safe and effective. Category III means there is insufficient data to permit classification as safe and effective. 37 Fed.Reg. 9464 (1972)(presently codified at 21 C.F.R. § 330.10).

The FDA issued its first formal position on PPA on January 15, 1985, when, as part of its Tentative Final Monograph for OTC products, the agency chose not to categorize PPA at all due to safety concerns. 50 Fed.Reg. 2220 (1985). The FDA deferred action on PPA again on August 23, 1994, because of unresolved safety issues. 59 Fed.Reg. 43386 (1994).

B. Pharmacology of PPA

PPA is a sympathomimetic amine, which means that it stimulates the sympathetic nervous system by mimicking the effects of molecules that regulate the system. FN3 Specifically, sympathomimetic amines are similar in structure to norepinephrine FN4 or epinephrine,FN5 which are both catecholamines produced by the body to regulate the nervous system. Amphetamine, ephedrine, cocaine, and PPA are examples of sympathomimetic amines. Sympathomimetic amines have similar chemical structures. For example, PPA's structure is nearly identical to amphetamine; PPA has a β-carbon hydroxyl group that amphetamine lacks. However, sympathomimetic amines are not identical and, consequently, may produce different effects or may be more or less potent. For example, although PPA is structurally similar to amphetamine, differing by only one hydroxyl group, it is far less potent than amphetamine.

FN3. The sympathetic nervous system is one part of the autonomic nervous system; the parasympathetic nervous system is the other part. The autonomic nervous system is automatic, i.e., it cannot be controlled by the mind. These systems work in balance with

each other and directly or indirectly affect the body. The sympathetic nervous system has an active pushing function; the parasympathetic has a relaxing function.

FN4. Norepinephrine is found in the brain and is the primary neurotransmitter in the sympathetic nervous system. Norepinephrine controls "fight or flight" reactions.

FN5. Epinephrine is a brain neurotransmitter and a major hormone in the body.

***3** The sympathetic nervous system is important in emergency situations that cause stress and require a "fight or flight" response. Common effects of the "fight or flight" response are increases in heart rate, increases in blood pressure, dilation of the trachea and bronchi, pupil dilation, and increases in blood flow to the brain, heart and skeletal muscles and decreases in blood flow to the skin and internal organs.

C. Physiology of PPA

The safety of PPA has long been controversial. C. Raymond Lake et al., *Adverse Drug Effects Attributed to Phenylpropanolamine: A Review of 142 Case Reports* 89 Am. J. Med. 195 (1990). Beginning in the late 1970s, case reports linking the use of products containing PPA to hemorrhagic stroke emerged. Waltern N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke,* 343 New Eng. J. Med. 1826 (2000). Affected patients were most commonly adolescent girls or young women between the ages of 17 and 45 years who had used appetite suppressants containing PPA. *Id.* Many of the case reports involved the first use of PPA-containing products. *Id.* In addition to case reports, the FDA received 22 spontaneous reports of hemorrhagic stroke associated with PPA in appetite suppressants in 16 cases and cough-cold remedies in six cases. *Id.*

Stroke is the third leading cause of death in the United States, behind only heart disease and cancer. More than 750,000 people suffer a stroke every year. It is the leading cause of serious long-term disability. Many survivors of stroke need help due to serious long-term disability. National Stroke Association, *Recovery and Rehabilitation* (2002).

Strokes are caused by a disruption in the flow of blood to the brain due to either an occluded blood vessel (ischemic stroke) or rupture of a blood vessel (hemorrhagic stroke). National Institute of Neurological Disorders and Stroke *Stroke Information Page* (July 1, 2001). Interruption in blood flow deprives the brain of nutrients and oxygen, resulting in death of the cells in the affected vascular territory of the brain. When brain cells die, function of the body parts they control is impaired and may result in paralysis, speech and sensory problems, memory and reasoning problems, coma, or death. American Heart Association *Heart and Stroke Statistics -2003 Update* (2003).

Ischemic stroke accounts for more than 85% of all strokes. Many people who experience ischemic stroke suffer from other health problems or conditions such as high blood pressure or hypertension and heart disease. Other factors that increase a person's risk of ischemic stroke are gender, race, and age. Another risk factor for ischemic stoke is arteriosclerosis (gradual cholesterol deposition). National Stroke Association, *Stroke Prevention* (1999). Sometimes the deposits of cholesterol narrow the arteries so much that blood cells may collect and form clots. Ischemic strokes can be caused when these blood clots block an artery. If the blockage occurs in an artery leading to the brain, a thrombotic stroke or cerebral infarction can occur. Almost 50% of strokes involve thrombosis. Sometimes a blood clot is formed within an artery outside the brain. If this blood clot dislodges, travels within the bloodstream, and becomes trapped in an artery closer to the brain an embolic stroke can occur.

***4** The second type of stroke is hemorrhagic stroke. National Institute of Neurological Disorders and Stroke *Stroke Information Page* (July 1, 2001). The release of blood by the sudden rupture of an artery within or surrounding the brain causes hemorrhagic stroke. *Id.* There are two types of hemorrhagic stroke: intracerebral and subarachnoid.

Intracerebral hemorrhage occurs when an artery within the brain bursts, allowing blood to leak within the brain. *Id.* The release of blood in the brain increases pressure within the brain and can damage the brain cells surrounding the released blood. The most common cause of intracerebral hemorrhage is hypertension.

Subarachnoid hemorrhage occurs when an artery near the brain ruptures and fills the area surrounding the brain with blood. *Id.* The release of blood, as in an intracerebral hemorrhage, creates an increase in pressure and can damage the brain cells surrounded by the blood.[FN6]

FN6. Subarachnoid hemorrhage can be caused by abnormalities of the arteries at the base of the brain (cerebral aneurysms). The cause of cerebral aneurysms is not known. Another cause of subarachnoid hemorrhage is cerebral arteriovenous malformation, which is a disorder in the blood vessels in the brain. The cause of arteriovenous malformation is also unknown. Arteriovenous malformation occurs when brain arteries connect directly to the veins, without having the normal capillaries between them

Two epidemiological studies examined the prevalence of hemorrhagic stroke among users of PPA. The first study examined the occurrence of cerebral hemorrhage in patients less than 65 years of age who filled prescriptions for PPA-containing products at local Group Health Cooperative pharmacies in the Puget Sound area from 1977 until 1981. During that period, 216,189 prescriptions for products containing PPA were filled. The investigators assumed that each person filling a prescription was at risk for cerebral hemorrhage for 30 days after the prescription was filled. The investigators then compared the risk of the patients who filled prescriptions against the relative risk of people who did not use PPA, The results of the study found that the "risk of cerebral hemorrhage ⋯ if present at all, is very small. H. Jick et al., *Phenylpropanolamine and Cerebral Hemorrhage,* The Lancet 1017 (May 5, 1984).

The next epidemiological study, conducted in the mid-1980s by Drs. O'Neill and Van de Carr, also found no significant association between PPA and stroke. This study was not published.

In 1991, Dr. Heidi Jolson, an FDA epidemiologist, reviewed the FDA's spontaneous adverse reaction reporting system. Dr. Jolson found that 22 spontaneous reports of hemorrhagic stroke associated with PPA had been reported to the FDA since the inception of the agency's computerized reporting system in 1969. Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke,* 343 New Eng. J. Med. 1826 (2000). Sixteen of the spontaneous reports involved appetite suppressants. *Id.* Nearly all of the reports involved women. Dr. Jolson concluded that the spontaneous reporting suggested that products containing PPA increased the risk of stroke. Dr. Jolson commented that a case-control study of hemorrhagic stroke in women would be the most feasible approach to test the hypothesis; neither clinical trials nor cohort studies would be feasible because of the low incidence of stroke in the population.

1. HSP and Risk

***5** The case reports and Dr. Jolson's review of the FDA's spontaneous reporting system raised significant concerns and controversy in the medical community and within the FDA. "[H]owever, it was not possible to prove or disprove an association" between PPA and an increased risk of hemorrhagic stroke. 66 Fed.Reg. 42665 (2001). A case-control study of hemorrhagic stroke, as Dr. Jolson remarked in her review, was a feasible way of proving or disproving the suspected association. For this reason, Yale University School of Medicine, the FDA, and some manufacturers of PPA collaborated to design a case-control study [FN7] of men and women, 18 to 49 years of age, to examine the possible relationship between ingestion of PPA and stroke. The study was named the Hemorrhagic Stroke Project ("HSP").

FN7. The HSP identified two groups of individuals: a group of individuals who had a stroke (cases) and a group of people who had not had strokes (controls). "Case-control studies measure and compare the frequency of exposure in the group with the disease 'the cases' and the group without the disease 'the controls. This is different from a cohort study, which measures and compares the incidence of disease in the exposed and unexposed control group. *See* Reference Manual on Scientific Evidence at 340 (2d ed. Federal Judicial Center 2000).

The HSP conducted a case-control study that sought to determine whether individuals who suffered strokes were more likely to have ingested PPA. Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke*, 343 New Eng. J. Med.1826, 1826-32 (2000). If ingestion of PPA was in fact related to stroke, the prevalence of ingestion of PPA among the cases -people who had strokes - will be higher than that among the controls -people who had not had strokes. Thus, an association between PPA ingestion and stroke would exist if the prevalence of ingestion is higher in persons who have stroke than in those who do not.

Case-control studies, like the HSP, are often used when a study must be done quickly or inexpensively, or when the disease being studied is rare, e.g., less than 5% of the population. *Id.* at 343, 809 A.2d 77. In a case-control study the case group and the control group are selected on the basis of the outcome, i.e., having the disease of interest versus not having the disease of interest. *Id.* at 342, 809 A.2d 77. A case-control study compares the groups in terms of their frequency of past exposure to possible risk factors. Thus, a case-control compares the risk of having the "risk factor."

A case-control study cannot determine the actual risk or relative risk FN8 because the underlying population is not known. However, an estimate of the relative risk of the outcome, known as the "odds ratio," can be determined in a case-control study. *Id.* at 350, 809 A.2d 77.

FN8. The relative risk is the ration of the risk in the exposed group to the risk in the unexposed group. If the risks in the exposed group and unexposed group are the same, the relative risk will equal one. If the risks in the two groups are not the same, the relative risk provides a way of showing in relative terms how much different (greater or smaller) the risk for the exposed group is.

The odds ratio can be a very good estimate of the risk ratio that would have been obtained from a prospective cohort study. *Id.* The odds ratio is calculated by dividing the odds of exposure in the diseased group by the odds of exposure in the non-diseased group. *Id.*

The HSP patients were identified between December 1994 and July 1999 from 43 hospitals in six states. Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke*, 343 New Eng. J. Med. 1826, 1826-32 (2000). To be eligible, a patient had to be identified with symptomatic subarachnoid or intracerebral hemorrhage and able to communicate and complete the interview within 30 days after the stroke. *Id.* The HSP investigators also required absences of a history of either a brain lesion or stroke among patients.

***6** The HSP had four objectives:

(1) to estimate the association between PPA and hemorrhagic stroke among men and women between 18 and 49 years of age;

(2) to estimate the association between PPA and hemorrhagic stroke by type of PPA exposure among men and women between 18 and 49 years of age;

(3) to estimate the association between first use of PPA and hemorrhagic stroke among women between 18 and 49 years of age; and

(4) to estimate the association between PPA in appetite suppressants and hemorrhagic stroke among women between 18 and 49 years of age.

The HSP results suggest that PPA increases the risk for hemorrhagic stroke. Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke,* 343 New Eng. J. Med. 1826 (2000). Moreover, the investigators concluded that PPA in appetite suppressants was an independent risk factor for stroke in women between 18 and 49 years of age. *Id.* The results obtained in the HSP are degrees of statistical relationship existing between the cases and controls. The statistics obtained through the HSP were evaluated to determine whether an association existed between between PPA use and stroke. The HSP was originally scheduled for publication in the December 21, 2000, issue of *The New England Journal of Medicine.* The results of the HSP were not released to the FDA until May 11, 2000, however, because of the potential clinical and public health implications.

The HSP study suggests the following:

(1) That PPA in appetite suppressants is an independent risk factor for hemorrhagic stroke in women;

(2) An association for first-time users of cough-cold remedies containing PPA and stroke;

(3) That the use of cough-cold remedies containing PPA is possibly an independent risk factor for hemorrhagic stroke in women;

(4) No increased risk of hemorrhagic stroke in association with the use of cough-cold remedies containing PPA in men.

The HSP underwent several levels of medical and scientific peer review, e.g., by the FDA, *The New England Journal of Medicine,* and *Neurology.* The HSP results supported concerns within the medical community that PPA was associated with an increased risk of hemorrhagic stroke in men and women between 18 and 49, and even more importantly, that PPA in appetite suppressants could cause hemorrhagic stroke in women.

2. Food and Drug Administration Requests the Voluntary Withdrawal of all products containing Phenylpropanolamine

On November 6, 2000, in response to the HSP results, the FDA announced its intention to ban any OTC products containing PPA and asked firms that market products containing PPA to voluntarily discontinue marketing them. On August 14, 2001, the FDA published in the Federal Register its Proposal to Withdraw Approval for PPA-containing products because of the association of PPA with increased risk of hemorrhagic stroke. 66 Fed.Reg. 42665 (2001).

I. PARTIES' CONTENTIONS

A. Defendants' Challenge to Plaintiffs' Proposed Experts

*7 Defendants challenge the admissibility of testimony from eighteen (18) experts. The plaintiffs proffered experts include neurologists, pharmacologists, cardiologists, epidemiologists, and toxicologists. The court will briefly summarize the credentials and conclusions of each expert, his field of expertise, and the nature of the expert's intended testimony.

1. Dr. Steven Levine

Dr. Steven R. Levine is a board certified neurologist and is a Professor of Neurology and Director of Cerebrovascular Education at The Mount Sinai School of Medicine and Medical Center in New York City. Prior to his appointment at The Mount Sinai School of Medicine, Dr. Levine was the Detroit area principal investigator for the National Institute of Health and served as the co-chair of both the Michigan stroke Initiative and the America stroke Association Operation Stroke Detroit. Dr. Levine seeks to testify that PPA causes stroke in some people. Dr. Levine relies upon the HSP, medical literature, case reports and other evidence to support his conclusion that PPA can cause stroke in some people. Dr. Levine has advanced several lines of evidence that he believes suggest that PPA can cause stroke in some people including biological plausibility, temporal association, dose-response, epidemiological studies, pharmacological studies, animal models, textbooks, and other various levels of evidence that suggest an association between PPA and stroke. These lines of evidence focus on the factors considered when assessing causality, e.g., temporality, congruence, consistency, and plausibility, and, as a result, bolster Dr. Levine's testimony.[FN9]

FN9. Sir Austin Bradford Hill in 1965 published nine factors that are used to assess causality of disease. Austin Bradford Hill, *The Environment and Disease: Association or Causation?* 58 Proceedings of the Royal Society of Medicine 295-300 (1965). See also pg. 23 of this opinion.

2. Dr. Paul M. Wax

Dr. Paul M. Wax is dually board certified in emergency medicine and medical toxicology. Dr. Wax relies upon mechanisms of action, medical literature, biological plausibility, analogy to other sympathomimetics, and other evidence to support his conclusion that PPA can cause both hemorrhagic and ischemic stroke. Dr. Wax also draws conclusions through extrapolation of results. Specifically, Dr. Wax uses extrapolation to support his conclusions regarding different people of different age and gender.

3. Dr. Steven Pray

Dr. Pray is a Professor of Pharmacy. Dr. Pray focuses on non-prescription products and was the first professor in any pharmacy school in the nation devoted to this area. Dr. Pray discusses the alleged safety issues involving PPA, including the risk of hemorrhagic stroke, in his textbook *Non-Prescription Products Therapeutics* (Lippincott Williams & Wilkins 1999). Dr. Pray seeks to testify about warning issues and about how consumers respond to warnings. Dr. Pray also seeks to testify that more actions should have been taken to protect consumers of OTC products that contained PPA. Dr. Pray is not being offered as a causation expert.

4. Dr. Jerome Avorn

Dr. Avorn is a board certified internist and the chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at the Brigham and Women's Hospital at Harvard University School of Medicine. Dr. Avorn opines that PPA causes hemorrhagic stroke in susceptible men and women. Dr. Avorn also opines that PPA can cause stroke in children, young adults, and adults older than those studied in the HSP. Dr. Avorn reaches his conclusions regarding PPA on the basis of his education, training, clinical experience, and the lines of evidence discussed above.

5. Dr. Richard W. Clapp

***8** Dr. Clapp is an environmental epidemiologist. He is currently a Professor at the

Boston University School of Public Health and has published extensively in the field of Epidemiology. Dr. Clapp opines that the Yale study is valid and reliable. He further opines that PPA causes stroke. Dr. Clapp reaches his conclusions regarding PPA on the basis of his education, training, expertise, the HSP, and the lines of evidence discussed above.

6. Dr. Robert Egan

Dr. Egan is a board certified neurologist. Dr. Egan opines that PPA causes stroke based on a number of case reports. Dr. Egan reaches his conclusions regarding PPA on the basis of his education, training, clinical experience, treatment of stroke patients, and the lines of evidence discussed above.

7. Dr. Edward Feldman

Dr. Feldman is a physician and was a co-investigator of the HSP and coauthored the article describing its results. In addition, Dr. Feldman has been the lead or local investigator in several clinical trials involving stroke. Dr. Feldman opines that PPA causes hemorrhagic stroke in susceptible individuals, regardless of age, gender, dose or product type and that PPA is a substantial contributing factor in causing hemorrhagic stroke in people with arteriovenous malformation ("AVM"), aneurysm, and hypertension. Dr. Feldman reaches his conclusions regarding PPA on the basis of his own clinical research, experience, education, and the lines of evidence discussed above.

8. Dr. Steven Kittner

Dr. Kittner is a neurologist and an epidemiologist and is currently a Professor of Neurology at the University of Maryland Department of Medicine and at the Department of Epidemiology and Preventative Medicine. Dr. Kittner, at the request of the FDA, evaluated safety issues associated with PPA. Dr. Kittner opines that PPA can cause stroke in men and women. Dr. Kittner reaches his conclusions regarding PPA on the basis of his education, training, expertise, and the lines of evidence discussed above.

9. Dr. Raymond Lake

Dr. Lake is a board certified psychiatrist and a board certified clinical pharmacologist who has authored and co-authored several articles on PPA. Dr. Lake has also conducted studies involving PPA and its effects. Dr. Lake opines that PPA causes hypertensive crisis, seizures, strokes, and death in humans. Dr. Lake also seeks to comment on labels on PPA products. Dr. Lake reaches his conclusions regarding PPA on the basis of his education, training, clinical experience, his own research and writings, and the lines of evidence discussed above.

10. Dr. James McDowell

Dr. McDowell is a board certified neurologist who is currently the Medical Director of the Stroke Program and of Neurophysiology at Providence St. Peter Hospital in Olympia, Washington. Dr. McDowell has examined thousands of stoke patients. Dr. McDowell opines that PPA causes both hemorrhagic and ischemic strokes in some people including those with predisposing factors such as AVM, aneurysm, and hypertension. Dr. McDowell reaches his conclusions regarding PPA on the basis of his education, clinical experience, and the lines of evidence discussed above.

11. Dr. Walter J. Molofsky

*9 Dr. Molofsky is pediatric neurologist and is the Associate Chairman in the Department of Neurology, Institute for Neurology and Neurosurgery, Beth Israel Medical Center and Co-Director of Pediatric Neurology at Beth Israel Medical Center. Dr. Molofsky is also an Associate Professor of Neurology at Albert Einstein College of Medicine. Dr. Molofsky has treated between 180 to 300 children who suffered non-traumatic hemorrhagic stroke from 1996 until 2002. Dr. Molofsky opines that PPA is a risk factor for stroke in persons under the age of 18. Dr. Molofsky reaches his conclusions regarding PPA on the basis of his clinical experience, training, books on pediatrics and pediatric neurosurgery, and articles on strokes in children and cerebral vascular disease.

12. Dr. Paul Pentel

Dr. Pentel is a board certified medical toxicologist. Dr. Pentel is also a Professor of Medicine and Pharmacology at the University of Minnesota and serves as a Senior Physician and Chief of the Division of Clinical Pharmacology and Toxicology at Hennepin County Medical Center. Dr. Pentel reaches his conclusions regarding PPA on the basis of his education, training, research, clinical experience, and expertise.

13. Dr. George Ricaurte

Dr. Ricaurte is a licensed physician and board certified Diplomat in Psychiatry and Neurology. Dr. Ricaurte is an Associate Professor in the Department of Neurology, Johns Hopkins University School of Medicine. Dr. Ricaurte also has a Ph.D. in Pharmacology and Toxicology from the University of Chicago. Dr. Ricaurte's research focuses on amphetamine derivatives and their potential effects on the brain. Dr. Ricaurte has been an investigator or co-investigator for several research studies funded by the National Institute of Health and has authored or co-authored over 100 peer-reviewed articles dealing primarily with amphetamines and their neurotoxic potential. Dr. Ricaurte opines that PPA can cause stroke in some people. Dr. Ricaurte reaches his conclusion regarding PPA on the basis of his education, training, clinical experience, and expertise.

14. Dr. Stanley Tuhrim

Dr. Tuhrim is a board certified neurologist. Dr. Tuhrim has been a Fellow in the Stroke Council of the American Heath Association since 1984 and is a member of the American Academy of Neurology; National Stroke Association; American Medical Informatics Association; and the Society of Critical Care Medicine. Dr. Tuhrim has been an investigator or co-investigator in several research projects involving stroke and has authored or co-authored several articles that pertain to strokes. Dr. Tuhrim opines that PPA can cause stroke. Dr. Tuhrim reaches his conclusions regarding PPA on the basis of his education and his extensive practical experience treating stroke patients.

15. Dr. Alan Woolf

Dr. Woolf is a board certified pediatrician and also a board certified medical toxicologist. Dr. Woolf is also a Fellow in The Academy at Harvard Medical School and an Associate Professor in Pediatrics at Harvard Medical School. Dr. Woolf opines that PPA can cause hemorrhagic stroke. Dr. Woolf bases his opinions on case reports, studies, medical literature, and clinical experience.

16. Dr. Gary Zaloga

*10 Dr. Zaloga was a co-investigator of research on the behavioral and neurochemical effects of PPA. Dr. Zaloga opines that PPA is capable of causing acute hypertension. Dr.

Zaloga testified previously that PPA is capable of causing acute hypertension. *Glaser v. Thompson Medical Co.*, 32 F.3d 969 (6 Cir.1994). Dr. Zaloga bases his opinion on peer-reviewed scientific evidence, clinical and research experience.

B. Defendants' Contentions

Defendants stridently argue that PPA is safe and that there is no scientifically reliable proof that PPA causes hemorrhagic stroke, ischemic stroke, or any other injury. Defendants contend that because there is no scientifically reliable proof that PPA causes hemorrhagic stroke, ischemic stoke, or any other injury, the plaintiffs' experts' testimony of causation is inadmissible.

1. There is no reliable scientific evidence that PPA can cause hemorrhagic stroke

Sir Austin Bradford Hill in 1965 published nine factors that are used to assess causality of disease. Austin Bradford Hill, *The Environment and Disease: Association or Causation?* 58 Proceedings of the Royal Society of Medicine 295-300 (1965). These factors are used to assess causality of a disease. The Bradford Hill factors include whether: (1) a temporal relationship exists; (2) the association is strong or weak; (3) a dose-response relationship exists; (4) the results have been replicated; (5) the association is biologically plausible; (6) alternative explanations have been adequately considered; (7) the association exhibits specificity; and (8) the findings are consistent with other knowledge. *See* *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp.2d 584, 592 (D.N.J.2002)(citing the Bradford Hill factors). The defendants assert that the totality of scientific evidence does not satisfy the Bradford Hill criteria with respect to hemorrhagic stroke and, therefore, plaintiffs' experts' testimony that PPA cause hemorrhagic stroke should be inadmissible.

The defendants recognize that the plaintiffs' experts rely upon a variety of scientific evidence to supports their conclusions that PPA is associated with stroke. This evidence includes case reports and series; several textbooks and learned treatises; chemical structure analysis; animal studies; clinical studies; a retrospective stroke study; and the HSP. The defendants staunchly argue that notwithstanding this "evidence," plaintiffs' experts cannot satisfy the Bradford Hill criteria and, therefore, this court should not allow their causation testimony. The defendants strongly challenge the plaintiffs' experts' ability to satisfy four of the Bradford Hill criteria: biological plausibility, strength of association, temporality, and dose-response relationship.

a. No biological plausibility that PPA causes stroke

First, defendants assert that it is not biologically plausible that PPA causes hemorrhagic stroke. Defendants claim that the plaintiffs' experts' purported explanations about how acute increases in blood pressure, vasospasm, vasculitis, and vascular "beading" caused by PPA might induce hemorrhagic stroke is speculative and inconsistent with existing knowledge about the mechanisms that cause stroke. Defendants assert that there is no reliable scientific evidence that an acute blood pressure increase can cause a stroke. The defendants, similarly, defendants assert that there is no reliable scientific evidence that PPA can cause vasospasm, vasculitis, or beading.

***11** Next, the defendants highlight that acute increases in systemic blood pressure is a well accepted means of preventing ischemic stroke following a hemorrhagic stroke. Defendants also note that blood pressure increases equal or greater than those reported in studies cited by plaintiffs occur during normal daily activity. The autoregulatory system, according to the defendants, is equipped to handle these routine blood pressure increases. Defendants proffer that the autoregulatory system must also be capable of handling blood pressure increases following ingestion of PPA.

b. Odds ratios in the HSP are statistically non-significant

The defendants second challenge to the plaintiffs' experts testimony is that there is no strength of association between PPA and hemorrhagic stroke because the odds ratios obtained by the HSP investigators and published in the *New England Journal of Medicine* are weak and statistically non-significant. The defendants argue that because these odd ratios are statistically non-significant, the purported association between PPA and hemorrhagic stroke could be the result of confounding or biases.

c. Temporality cannot be established

Third, the defendants also contend that the plaintiffs' experts' testimony is scientifically unreliable because they did not establish that PPA was taken before the onset of "sentinel symptoms," including sentinel headache,[FN10] minor leak, or warning leak that often exist before a stroke occurs. The defendants argue that if sentinel symptoms existed before ingestion of PPA, temporality cannot be established, which is a crucial factor for a determination of causation. The epidemiological and toxicological evidence provided by the plaintiffs did not consider whether sentinel symptoms existed before the ingestion of PPA. Likewise, case reports and series generally did not consider whether sentinel symptoms existed. Thus, plaintiffs' experts, according to the defendants, cannot prove causation or even suggest an association because temporality cannot be established. The defendants also suggest that sentinel symptoms may also be a source of confounding; a person suffering from sentinel symptoms may have sought relieve through the use of PPA products, which would then be present when the stroke ultimately occurred, but not responsible for the stroke.

FN10. A sentinel headache often occurs before a subarachnoid hemorrhage. Some experts suspect that it is caused by a small subarachnoid hemorrhage or warning leak.

d. A dose-response relationship cannot be established

Fourth, the defendants claim that the plaintiffs' experts lack a very important factor in any assessment of cause and effect: dose-response relationship. For a dose-response relationship to exist, there must be a relationship between exposure and response. The defendants assert that there is no valid evidence of dose-response relationship; the only evidence that suggests a dose-response relationship, which is found in the HSP, was manipulated to suggest a trend in favor of a dose-response relationship according to the defendants.

2. There is no reliable scientific evidence that PPA can cause hemorrhagic stroke

***12** The defendants scrupulously critique all of the scientific evidence that the plaintiffs' experts rely upon even though it is the type of evidence that members of the scientific and medical community use and rely upon every day. The defendants' challenges to each category of evidence is set forth below.

a. Case Reports and Series

Case reports and series are "[t]he most basic type of descriptive study of an individual (case report) or a series of individuals (case series), usually including such factors as gender, age, and exposure or treatment, but without controlled assessment of the relationship between exposure or treatment and disease or outcome." Reference Manual on Scientific Evidence at 480 (2d ed. Federal Judicial Center 2000). Although the defendants acknowledge the pervasive use of case reports, they challenge the plaintiffs' experts' reliance upon them as a basis for their opinions that PPA causes stroke. A major deficiency of case reports and series is that they lack controls. As a result, case reports

cannot reveal whether an association actually exists because they "make little attempt to screen out alternative causes for a patient's condition." *Glastetter v. Novartis Pharm. Corp.*, 252 *F.*3d 986, 989-90 (8 Cir.2001). Defendants claim that case reports and series provide merely anecdotal evidence of clinical events. Likewise, Defendants argue that plaintiffs' experts' reliance upon textbooks is also misplaced because these books are no more reliable than the underlying evidence upon which they rely, i.e., case reports and series. *See Glastetter*, 107 *F.* Supp.2d 1015, 1034 (E.D.Mo.2000), *aff'd*, 252 *F.*3d at 993.

b. Chemical Structure Analysis

The effects of PPA are not identical to those of other sympathomimetic drugs. "[R]elatively minor modifications in the drug molecule may result in major changes in pharmacological properties." Louis S. Goodman et al., *The Pharmacological Basis of Therapeutics* 32 (10th ed.2001). Numerous courts have recognized this principle. *See, e.g.*, *Schudel v. General Elec. Co.*, 120 *F.*3d 991, 996-97 (9 Cir.1997)("[S]mall differences in molecular structure often have significant consequences.").

Defendants maintain that PPA's properties differ from those of other sympathomimetic drugs that are generally accepted risk factors for stroke. One significant reason for this difference, according to the defendants, is that PPA is substantially less potent than other sympathomimetic drugs. Defendants assert that the differences between PPA and other sympathomimetic drugs make extrapolation and comparison of PPA to other sympathomimetic drugs an unreliable basis for expert testimony that PPA can cause stroke.

c. Animal Studies

Defendants argue that plaintiffs' experts' reliance upon animal studies examining the effects of PPA on blood pressure or blood vessels and one study examining stroke in rats does not support the conclusion that PPA causes hemorrhagic stroke because animal study results must be extrapolated twice: once, from animals to humans and, again, from higher doses to lower doses. *See Reference Manual on Scientific Evidence*, supra, at 410. The need to extrapolate substantially limits the value of animal studies when attempting to prove or disprove whether an association between PPA and stroke exists. Consequently, some courts have held that animal studies are not a valid basis for extrapolating conclusions about human disease causation. *See e.g.*, *Magistrini*, 180 *F.*Supp.2d at 593. Moreover, the defendants suggest that the absence of a proper dose-response evaluation creates insolvable uncertainty: can the animal studies be extrapolated or is there a threshold no-effect dose? Thus, according to the defendants, animal studies cannot provide a reliable scientific basis for expert testimony in this case.

d. Rechallenge Data

***13** Defendants assert that the plaintiffs are unable to produce rechallenge data specific to stroke, which precludes sound determinations regarding the danger or safety of PPA. Accordingly, defendants argue that plaintiffs' experts' testimony should be inadmissible.

e. The HSP

The defendants assert that reliance upon an epidemiologic study does not, by itself, mean that expert testimony is admissible under Rule 702. For example, in *Magistrini*, the court granted a motion to exclude the testimony of an expert even though he offered fourteen (14) epidemiological studies in support of his claim. *Magistrini*, 180 *F.Supp.* at 592. The court held that these studies should be excluded because they

utilized questionable methodologies. *Id.* at 604; *cf.* *In re TMI Litig.*, 193 *F* .3d 613, 711 (3d Cir.1999) (finding epidemiological study to be unreliable). The defendants assert that the HSP should be excluded on similar grounds because the investigators used improper methodologies and, as a result, the HSP results are unreliable. The HSP, according to the defendants, also produced fragile results that could be entirely attributable to chance or due to confounding. Finally, the defendants assert that several types of bias adversely affect the reliability of the HSP.

(i) Methodology

Despite the amplitude of the defendants' challenges to the HSP design and the investigators' methodology one salient fact remains clear: the study was designed by one of the most prestigious universities in the world with input from the defendants and the responsible regulatory agency. Rarely, does such involvement occur during the design of an epidemiological study. The defendants' challenges to this "flawed" study should be considered in light of their role in the original design of the study.

The HSP involved 702 cases and 1376 controls. Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke,* 343 New Eng. J. Med. 1826 (2000). The defendants, relying upon *State v.. Fortin*, 162 *N.J.* 517, 525, 745 A.2d 509 (2000), claim that such a small number of cases and controls can not support reliable conclusions arguing that the results are fragile, prevent valid modeling,[FN11] and that the small numbers are indicative of flawed recruitment, e.g ., procedural failures and inadequate supervision of the random digit dialing program. Predominantly, the defendants claim that the two odds ratios that form the backbone of the HSP conclusion- "any use" of appetite suppressants in women (6 cases, 1 control) and "first use" of cough-cold products in women (7 cases, 4 controls) are not reliable because the conclusions are fragile, i.e., even a small error, confounder or bias can produce a substantial change in the odds ratio, confidence interval, and p-value.

FN11. The defendants suggest that a better approach would have been stratification or exclusion.

Second, the defendants argue that the investigators decision to combine intercerebral hemorrhagic stroke and subarachnoid hemorrhagic stroke is a fatal flaw because they are two distinct diseases.

***14** Third, the defendants argue that the purported findings of the HSP cannot be extrapolated to other subpopulations with any degree of scientific reliability.

Fourth, the defendants assert that the redefinition of "first use" halfway through the study was inappropriate. The defendants suggest that the change was made with knowledge of the impact upon the results for one reason: to increase the odds ratio, and consequently, any positive association between "first use" of PPA and hemorrhagic stroke. A more likely explanation is that the HSP investigators decided to redefine and shorten the definition of "first use" was made to coincide with the pharmacological half-life of PPA, which is short. The court is not convinced that the HSP investigators redefined "first use" to manipulate the date or its significance and, instead, finds that the HSP investigators redefined "first use" to reflect PPA's pharmacological properties.

(ii) Chance

The defendants claim that the HSP results are entirely attributable to chance. The defendants, again relying upon the small sample size, argue that the HSP's sole statistically significant elevated odds ratio relies on just 6 cases and 1 control. The only other odds ratio from which the HSP conclusions are drawn is for "first use" of PPA cough-cold products by women, which was not statistically significant. The HSP itself

called this nothing more than a "suggestion of an association." Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke,* 343 New Eng. J. Med. 1826, 1830 (2000). A finding of nothing more than a "suggestion of an association" is not a sufficient basis for admissible expert testimony.

When reported associations in case-control studies, such as the HSP, are based on small numbers of exposed cases and/or exposed controls, the result is wide confidence intervals. This is often referred to as "data fragility." A consequence of data fragility is that small errors or adjustments to the data can result in dramatically different results, sometimes changing the absence of an association to the presence of an association, or *vice versa.*

The strength of association between the ingestion of PPA and stroke is found in the odds ratios. Because the odds ratios obtained by the HSP investigators are not statistically significant the defendants argue that the strength of association is weak and the results can be attributed to chance. Thus, the defendants argue that the HSP cannot provide a scientifically reliable basis for expert testimony about causation. *See* *General Elec. Co. v. Joiner*, 522 *U.S.* 136, 145-146, 118 *S.Ct.* 512, 519, 139 *L.Ed.*2d 508, 519 (1997).

(iii) Confounding

The defendants also argue that the HSP results can be explained in whole or in part by confounding, one of the most common and important problems in observational epidemiological studies. The defendants assert that the HSP results for "first use" of PPA in women and for the use appetite suppressants that contain PPA in women were due to confounding and not a causal connection.

***15** Confounding occurs when a known risk factor for a disease is associated with the suspected factor considered by the study, but is not a result of the suspected factor. In their briefs, both parties evaluated a case-control study of the association between drinking coffee and cancer of the pancreas that was conducted in the early 1980s. The study found that coffee could be a carcinogen, specifically concluding that coffee might cause pancreatic cancer. B. MacMahon et al., *Coffee and cancer of the pancreas,* 204 New Eng. J. Med. 630, 630-33 (1981). Some members of the scientific community challenged the alleged association and suggested that it was the result of confounding by cigarette smoking. Consequently, two explanations for the alleged association existed: first, drinking coffee actually causes cancer of the pancreas; or the association between drinking coffee and cancer of the pancreas may be a result of confounding by cigarette smoking. Following an additional investigation, most of the scientific community agreed that the observed association of coffee drinking and cancer of the pancreas was the result of confounding because cigarette smoking is associated with coffee drinking and cigarette smoking is a known risk factor for cancer of the pancreas.

The defendants allege that education is a powerful confounding factor that was not taken into account. To address the effect of an individual's level of education and her risk of stroke, the defendants assert that the HSP investigators should have used the number of years of schooling completed as a continuous variable. Instead, the HSP investigators decided to use "high school graduate" as the only measure of the level of education. The defendants offer no evidence to support their claim that the adjustments for education caused residual confounding or that the investigators were motivated to analyze the preliminary data to reach a finding of an association. Consequently, this court is not convinced that the absence of a continuous variable created confounding, such that use of a continuous variable would have explained the observed association. Perhaps, using a continuous variable for the number of years of schooling would have improved the HSP. However, failure to use a continuous variable does not negate its findings.

(iv) Bias

The defendants contend that three types of bias (misclassification, selection, and information) impaired the HSP. Biases can be a severe problem in a case-control study because they can greatly affect the results, even when great effort is taken to eliminate them.

The first bias that the defendants argue impairs the HSP is misclassification of exposure to PPA. According to the defendants, misclassification occurred because some of the cases or controls that were actually exposed were erroneously classified as unexposed, and some who were actually not exposed were erroneously classified as exposed. However, misclassification generally results in an underestimation of the true risk of the disease associated with the exposure. Leon Gordis, *Epidemiology* (2d ed.2000).

***16** The second bias that the defendants argue renders the HSP unreliable is selection bias. The defendants claim that the HSP's low overall response rate renders the HSP scientifically unreliable because the apparent association between PPA a stroke could be due to selection bias. If the way that cases and controls are selected is such that an apparent association is observed - even if, in reality, exposure and disease are not associated - the apparent association is the result of selection bias. Selection bias can occur from the non-response of potential controls. Conceivably, the people who did not respond to the study differ from those who did in regard to demographic, socioeconomic, cultural, and other characteristics. *See* E. Ronmark et al., *Non-responders to a postal questionnaire on respiratory symptoms and disease*, 15 Eur. J. Epidemiol. 292, 293-99 (1999). The defendants claim that the HSP results were rendered unreliable by selection bias because limited, if any, information was obtained from the non-responders. Thus, the defendants argue that non-response introduced a serious bias that renders the HSP scientifically unreliable since there is no scientific basis to believe that the study obtained a representative sample of people without the disease.

The court finds that the HSP investigators applied similar methods during the recruitment of cases and controls and sought perfectly matched controls; imperfectly matched controls were only used to prevent exclusion of a case from the study. Moreover, the investigators required all control subjects be interviewed within 30 days to lessen selection bias. Thus, the court finds that the HSP has not been rendered unreliable by selection bias. The court is also finds that the HSP has not been rendered unreliable by information bias.

3. There is no reliable scientific evidence that PPA can cause ischemic stroke

Defendants argue that there is no reliable scientific evidence exists that establishes an association between PPA and ischemic stroke. Thus, the Bradford Hill criteria are not reached so it is not necessary for the court to consider the application of the Bradford Hill criteria with respect to ischemic stroke.

4. There is no reliable scientific evidence that PPA can cause any other injury

Defendants assert that there is no reliable scientific evidence of an association between PPA and any other injury. Consequently, defendants argue that it is not necessary for the court to consider the application of the Bradford Hill criteria with respect to those injuries.

C. Plaintiffs' Contentions in Opposition

Plaintiffs, in response to the defendants' contentions, claim that their experts based their opinions on the type of evidence normally relied upon by experts in forming opinions including personal observations, evidence admitted at trial, and the type of data normally relied upon by experts in forming opinions on the same subject. *Biunno*,

N.J.Rules of Evidence, comment 1 on *N .J.R.E.* 703 (2003). The plaintiffs' experts relied upon case reports and series, studies, textbooks, clinical symposia, guidelines, panels, adverse drug event reports ("ADE"), and other evidence when making their causality determinations. Different types of evidence were given different weight by the experts. Plaintiffs' contend that their experts have used sound methodology and reliable scientific evidence in reaching their opinions. Consequently, plaintiffs argue that their experts' testimony should be admissible. The plaintiffs' contentions are discussed in greater detail below.

1. The HSP is reasonably relied upon by experts in the field

***17** The HSP has been peer-reviewed by the medical and scientific community three times. First, the FDA reviewed the HSP and found it "demonstrated a statistically significant increased risk of hemorrhagic stroke among appetite suppressant users and first time users of PPA as a cough-cold remedy." Walter N. Kernan et al., *Phenylpropanolamine and the Risk of Hemorrhagic Stroke,* 343 New Eng. J. Med. 1826, 1826-32 (2000). Moreover, the FDA concluded that the HSP provided compelling evidence of increased risk of stroke in some people despite the defendants assertions that the HSP results are fragile or based on small sample size.

Second, the prestigious *New England Journal of Medicine* reviewed the HSP and, following a two-tailed analysis consistent with the journal's publication policy, concluded that the HSP results suggest that PPA may be associated with stroke. The *New England Journal of Medicine* published the HSP as its lead article in December 2000.

Finally, *Neurology* published a peer-reviewed article based on the other data and findings from the HSP pertaining to the dietary supplement Ephedra. [FN12] Plaintiffs assert that in light of the substantial level of evaluation and examination that the HSP has undergone, it is reasonable for experts in the medical and scientific communities to rely upon the HSP when analyzing PPA's association with stroke.

FN12. L.B. Morgenstern et al., *Use of Ephedra-Containing Products and Risk for Hemorrhagic Stroke,* 60 Neurology 132 (2003)

2. Scientific literature is reasonably relied upon by experts in the field

The plaintiffs assert that their experts reasonably relied upon the extensive volume of scientific literature that supports the conclusion that PPA is associated with stroke. In addition to the HSP, the plaintiffs rely upon a variety of scientific literature including: hundreds of case reports and series; several textbooks and learned treatises; chemical structure analysis; animal studies; several clinical studies; and a retrospective stroke study.

a. Case Reports and Series

Case reports and series, according to plaintiffs, can be considered reliable evidence on causation when experts in the particular field reasonably rely upon case reports. *See State v. Smith*, 262 *N.J.Super.* 487, 511, 621 A.2d 493 (App.Div.1991), *certif. denied* 134 *N.J.* 476, 634 A.2d 523 (1993). In many scientific disciplines, the use of case reports is longstanding, as evidenced by the continued publication of such reports in peer-reviewed scientific journals. *Reference Manual on Scientific Evidence,* supra, at 469. Plaintiffs remark that case reports are commonly published in medical journals to alert clinicians of possible health problems. Plaintiffs argue that experts can properly rely upon a single well-investigated case report for causation opinions. However, this issue is not before the court; hundreds of case reports questioning the safety of PPA in OTC products exist. *See* C. Raymond Lake et al., *Adverse Drug Effects Attributed to*

Phenylpropanolamine: A Review of 142 Case Reports, 89 Am. J. Med. 195, 208 (1990). Moreover, case reports and case series are not the only type of scientific literature that provides support for the plaintiffs' experts' opinions.

b. Textbooks and Treatises

***18** Plaintiffs' experts cite several textbooks including *Ischemic Cerebrovascular Disease*, (Oxford University Press 2001), *Rosen's Emergency Medicine: Concepts and Clinical Practice*, (5 ed 2001), and *Little Black Book of Neurology*, (4 ed 2002), that specifically list PPA as a possible cause for hemorrhagic or ischemic stroke. Medical textbooks and treatises are considered reliable authority and may be relied upon by experts in the field. *See* *Morlino v. Med. Ctr. of Ocean County*, 152 *N.J.* 563, 706 A.2d 721 (1997).

c. Chemical Structure Analysis

Plaintiffs' experts also rely upon the similarities of PPA's structure to that of other sympathomimetics including amphetamine and cocaine. Toxicologists and pharmacologists routinely consider an observed effect of similar drugs to infer that other similar drugs may also cause the same effect because scientists recognize that similar chemical may have similar properties, according to the plaintiffs.

In this case, Plaintiffs claim that PPA and other sympathomimetic drugs cause similar side effects including: elevation in blood pressure, headache, stroke, seizure, psychic disturbances, and death. Defendants concede that PPA is a sympathomimetic that can cause elevations of bloods pressure at particular levels, but argue that although PPA may have some properties of other sympathomimetics, it also has substantial differences. Plaintiffs agree with the defendants that all sympathomimetic drugs do not produce all of the same side effects. However, plaintiffs in opposition state that it is accepted that these drugs constrict blood vessels and cause strokes. In particular, plaintiffs explain that PPA and other sympathomimetic drugs can cause transient and diffuse constrictions or isolated rings of contraction in blood vessels. When viewed on a cerebral angiogram with radio-opaque dye, these constrictions can look like a string of beads-hence the term "beading." Beading has been observed with many sympathomimetic drugs, including PPA. These observations have been published in peer-reviewed literature. *See e.g.*, Carlos S. Kase et al., *Intracerebral Hemorrhage, in Neurology in Clinical Practice: The Neurological Disorders*, 1032-1047 (2d ed.1996).

Moreover, plaintiffs point out that analogizing one drug to other similar drugs is routinely performed in certain scientific disciplines, e.g., toxicology and pharmacology. The plaintiffs conclude by offering that their experts' use of this technique is appropriate in this case.

d. Animal Studies

Plaintiffs' experts also rely on published, controlled animal studies. "Toxicological research often involves exposing animals ⋯ to chemicals, monitoring the outcomes, and comparing the outcome with those for unexposed control groups." *Reference Manual on Scientific Evidence*, supra, at 405. Toxicological research often provides the best scientific evidence about the risk of a disease from chemical exposure and the metabolic, cellular, and other physiological effects of chemical exposure because "it is often unethical to experiment on humans by exposing them to known doses of chemical agents." *Id.* However, the extent to which animal studies can provide useful information is debatable because the results must be extrapolated twice: once, from animals to humans and, again, from higher doses to lower doses. *Id.* at 410, 706 A.2d 721. Extrapolation from one species to another presents several obstacles. For example, "differences in absorption, metabolism, and other factors may result in interspecies variation in response." *Reference Manual on Scientific Evidence*, supra, at 346.

Nonetheless, scientists often find the first extrapolation appropriate.

*19 Extrapolation from higher doses to lower doses presents a substantially more challenging problem because one of the three central tenets of toxicology is that "the dose makes the poison," i.e., all chemical agents are hazardous, whether they cause harm is a question of dose. *Id.* at 403. Consequently, the extrapolation of animal study results involving higher doses of a chemical to humans exposed to lower doses of the same chemical creates insolvable uncertainty: can the animal studies be extrapolated or is there a threshold no-effect dose? Thus, the admissibility of toxicological expert testimony can be controversial. *Id.* at 414. However, in this case, the animal studies complement the HSP by considering other information that is relevant to the assessment of causation including mechanisms of action and the specificity of response. Plaintiffs, therefore, argue that it is appropriate for their experts to rely upon animal studies.

e. Clinical Trials

Plaintiffs' experts also rely on human clinical trials. *E.g.*, Paul R. Pentel *Toxicity of Over-the-Counter Stimulants*, 252 JAMA 1898 (1984); J.D. Horowitz et al., *Hypertensive Reponses Induced by Phenylpropanolamine in Anorectic and Decongestant Preparations*, 8159 The Lancet 60, 61 (1980); Steven C. Dilsaver et al., *Complications of Phenylpropanolamine*, 39(4) Am. Fam. Physician 201, 201-06 (1989). The most common adverse effect of PPA in these clinical trials was a sudden rise in blood pressure.

Other clinical trials have examined the potential synergistic effects of PPA and caffeine, specifically studying the combinations ability to cause transient hypertension. C. Raymond Lake et al., *Transient Hypertension after Two Phenylpropanolamine Diet Aids and the Effects of Caffeine: A Placebo-Controlled Follow-Up Study*, 86 Am. J. Med. 427, 427-32 (1989). The plaintiffs' experts contend that transient blood pressure spikes can cause hemorrhagic stroke while conceding that the precise mechanism of action is unknown.

f. Retrospective Stroke Study

The plaintiffs' experts also rely upon a retrospective analysis of more than 1,700 stroke patients who were admitted to the National Institute of Neurology and Neurosurgery in Mexico City, Mexico from 1986 until 1997. Jose Luis Ruiz-Sandoval et al., *Intracerebral Hemorrhage In Young People: Analysis of Risk Factors, Location, Causes, and Prognosis*, 30 Stroke 537, 541 (1999). The study concluded that "the use of phenylpropanolamine was responsible" for seven cases of intercerebral hemorrhagic stroke. *Id.*

g. Rechallenge Data

Plaintiffs cannot produce rechallenge data specific to stroke for ethical reasons. However, Dr. Lake noted a rechallenge event involving a 28 year-old female psychiatric patient who ingested more than four times the recommended amount of PPA and less than one day later suffered paranoid psychosis and a grand mal seizure. C. Raymond Lake et al., *Adverse Drug Effects Attributed to Phenylpropanolamine: A Review of 142 Case Reports*, 89 Am. J. Med. 195, 205 (1990). Rechallenge with PPA caused recurrence of some of her symptoms. Dr. Lake closed his article by writing, "Although conclusive statements about the danger or safety of PPA are still premature, caution appears prudent ⋯ conscientious attention to PPA ADRs will heighten physician awareness and will serve to resolve this controversial issue." *Id.* at 206.

3. Differential Diagnosis Is Routinely Performed by Experts in The Field

*20 Physicians, according to plaintiffs, routinely use differential diagnosis as a method of opining on causation of a disease. Differential diagnosis is a process by which different possible causes or risk factors for a disease are systematically considered, tested for and ruled in or ruled out. The New Jersey Supreme Court in *Rubanick* recognized that differential diagnosis is not a novel method. *Rubanick v. Witco Chem. Co.*, 125 *N.J.* 421, 450-451, 593 A.2d 733 (1991). Plaintiffs suggest that differential diagnosis is an appropriate methodology when opining on causation of a disease regardless of whether the opinion is reached for expert testimony or patient treatment.

4. The Bradford Hill Criteria Are Routinely Used when Considering Cause-Effect Relationships

As explained earlier, the Bradford Hill criteria are used to assess causality of disease. *See* Austin Bradford Hill, *The Environment and Disease; Association or Causation?* 58 Royal Society of Medicine 295-300 (1965). Today, ten causality factors, which include the original nine Bradford Hill factors, are often used to assess causality: consistency, congruence, strength of association, sensitivity, specificity, temporality, dose-response, plausibility, experiments and research, and analogy. Plaintiffs argue that their contention that PPA causes stroke can be supported by several of the Bradford Hill factors.

First, relying heavily upon the HSP, plaintiffs claim that the statistically significant increased risk of hemorrhagic stroke among appetite suppressant users and first-time users of PPA as a cough-cold remedy is indicative of strength of association. Second, the plaintiffs claim that the HSP found a temporal relationship between the time of ingestion and the onset of stroke. Third, the plaintiffs claim that the number of reports of hemorrhagic stroke following PPA use among young people suggests specificity. Fourth, the plaintiffs claim that clinical and animal evidence and the HSP findings are consistent with a dose-response relationship.

Fifth, the plaintiffs assert that it is biologically plausible that PPA cause stroke through vasoconstriction. Sixth, the plaintiffs claim that the evidence suggests coherence. Finally, plaintiffs assert that PPA is structurally and biologically analogous to other sympathomimetics that are generally accepted to cause stroke.

D. Defendants' Response to Plaintiffs' Contentions

The defendants submitted a reply brief in further support of their motion to exclude plaintiffs' experts' testimony. This reply brief echoes the arguments raised by the defendants' first brief.

III. LEGAL STANDARD

This litigation involves proof of the causal connection between PPA and stroke. In order to prevail, plaintiffs must prove factual causation by a preponderance of the evidence. The plaintiffs' case requires expert testimony to satisfy their burden with respect to both general causation and specific causation.

In this case, "general causation" addresses whether sound methodology supports plaintiffs' experts' opinions that PPA is capable of causing stroke. "Specific causation" addresses whether sound methodology supports and individual plaintiff's experts' opinions that PPA caused the plaintiff's stroke.

*21 Accordingly, the strength of the causation evidence available is of paramount concern. This court is charged with making a determination of the reliability and admissibility of the evidence provided by the plaintiffs. The proffered evidence includes epidemiological evidence, case reports, medical treatises, toxicological studies, and

various actions taken by the FDA.

A. New Jersey Law of Evidence and Experts

The defendants bring this motion seeking to exclude the opinions of all plaintiffs' general causation experts who opined that PPA in appetite suppressants and cough-cold products causes stroke or other injuries. They argue that none of these experts are qualified to testify, as no sound science exists to demonstrate that PPA causes these injuries. Thus, any expert opinions offered by plaintiffs should be excluded pursuant to New Jersey Rules of Evidence 702 and 703.

New Jersey Rule of Evidence 104(a) entrusts the evaluation and determination of the admissibility of all evidence with the trial court. N.J.R.E. 104. To do this, the New Jersey Supreme Court has charged trial courts with the responsibility in certain circumstances with conducting an evidentiary hearing, even when the parties do not request a Rule 104 hearing, in cases in which "the scientific reliability of an expert's opinion is challenged and the court's ruling on admissibility may be dispositive of the merits." *Kemp*, 174 *N.J.* at 425-27, 809 A.2d 77.

Accordingly, this court determined that in order to resolve this argument and determine the admissibility of expert testimony that PPA in appetite suppressants and cough and cold products is capable of causing stroke in humans Kemp hearings must be held. Case Management Order No. 7 (January 16, 2003).

"The admissibility of an expert's testimony and ultimate conclusions ⋯ will depend upon the expert's ability to explain pertinent scientific principles and to apply those principles to the formulation of an opinion; thus, the key to admission of the opinion is the validity of the expert's reasoning and methodology." *Landrigan v. Celotex Corp.*, 127 *N.J.* 404, 414, 605 A.2d 1079 (1992). Moreover, before expert testimony is permitted, it must be shown that proposed expert's testimony would be reliable. The rationale for this requirement is that expert testimony seeks to assist the trier of fact. An expert opinion that is not reliable is of no assistance to anyone. *State v. Kelly*, 97 *N.J.* 178, 478 A.2d 364 (1984).

New Jersey Rules of Evidence 702 and 703 are the starting points for determining whether the conventional general acceptance test of reliability should be the standard for the "admissibility of expert testimony relating to new or developing theories of causation in toxic-tort litigation." *Lindquist v. City of Jersey City Fire Dept.*, 175 *N.J.* 244, 814 A.2d 1069 (2003)(quoting *Rubanick v. Witco Chem. Corp.*, 125 *N.J.* 421, 593 A.2d 733 (1991)). Rule 702 provides:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education may testify thereto in the form of an opinion or otherwise.

*22 [*N.J.R.E. 702.*]

Rule 703 allows an expert meeting Rule 702's criteria to testify "if the facts or data are of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject." *N.J.R.E. 703*

In order for expert testimony to be admissible, it must meet three criteria: (1) the intended testimony must concern a subject matter that is beyond the ken of the average juror; (2) the field testified to must be at a state of the art such that an expert's testimony could be sufficiently reliable; and (3) the witness must have sufficient

expertise to offer the intended testimony. *Landrigan*, 127 *N.J.* at 413, 605 A.2d 1079 (citing *State v. Kelly*, 97 *N.J.* 178, 208, 478 A.2d 364 (1984)).

Ten years ago, the United States Supreme Court declared a standard where several factors were to be considered in determining the admissibility of new scientific evidence. *Daubert v. Merrell Dow Pharm., Inc.*, 509 *U.S.* 579, 113 *S.Ct.* 2786, 125 *L.Ed* 2d 469 (1993). The *Daubert* factors are: (1) whether the method can and has been tested; (2) whether it has been subjected to peer review; (3) the known or potential error rate; and (4) whether it has gained acceptance within the relevant scientific community. *Id.*

Since the Supreme Court's decision in *Daubert* was based on the language of Federal Rule of Evidence 702 and not grounded in a constitutional right mandating adoption by the states, individual states were not required to apply this standard. New Jersey courts, which had previously adhered to the "general acceptance" standard as expressed in *Frye v. United States*, 293 *F.* 1013 (D.C.1923) [FN13] never adopted *Daubert*, a standard that some federal courts recognize as having restrictive results. "In an attempt to prohibit the presentation of junk science to the trier of fact, perhaps *Daubert* has raised the bar for admissibility of expert testimony too high." *Siharath v. Sandoz Pharm. Corp.*, 131 *F.Supp.*2d 1347, 1373 (N.D.Ga.2001). "Maybe there should be a middle ground between the *Daubert* standard and a standard that would allow sympathetic plaintiffs with catastrophic injuries to recover against pharmaceutical manufacturers based upon nothing more than speculation and conjecture." *Id.* It is clear that the New Jersey standard is that middle ground, ensuring fair and objective standards when correctly applied by the court.

FN13. New Jersey still applies the *Frye* general acceptance standard in criminal cases.

New Jersey's extensive industrial legacy and the plethora of toxic-tort litigation that grew out of that history caused New Jersey courts to create such a "middle ground" with equity and practicality for admissibility of scientific evidence. Because toxic tort litigation historically implicated multiple or complex causation factors or involved long-term exposure to toxic substances, this area of litigation brought forth issues wrought with disagreement in the scientific community. In the toxic-tort context, "proof that a defendant's conduct caused the ⋯ injuries is more subtle and sophisticated than proof in cases concerned with more traditional torts." *Vassallo v. American Coding & Marking Ink Co.*, 345 *N.J.Super.* 207, 214-215, 784 A.2d 734 (App.Div.2001). As such, it was not always possible for plaintiffs to show "general acceptance" in order to prove scientifically, the cause of an injury.

***23** Recognizing a need for a broader standard due to the "extraordinary and unique burdens facing plaintiffs who seek to prove causation in toxic-tort litigation" and the "extremely high level of proof required before scientists will accept a new theory," New Jersey courts consequently adopted a new less restrictive standard. *See* *Rubanick*, 125 *N.J.* at 421, 593 A.2d 733. The *Rubanick* Court noted that "plaintiffs in toxic-tort litigation, despite strong and indeed compelling indicators that they have been tortiously harmed by toxic exposure, may never recover if required to await general acceptance by the scientific community of a reasonable, but as yet not certain, theory of causation." *Id.* at 434, 593 A.2d 733.

Rubanick was a consolidated toxic-tort case filed by survivors of two chemical plant employees. Plaintiffs alleged that the decedent employees' colon cancer was caused by workplace exposure to polychlorinated byphenals and heat transfer fluids. Applying New Jersey's "general acceptance" test, the trial judge ruled the plaintiff's expert's testimony unreliable, and granted defendant's motion for summary judgment on the issues of general and medical causation. The Appellate Division reversed. The case then went to the New Jersey Supreme Court, which held:

[I]n a toxic-tort litigation, a scientific theory of causation that has not yet reached general acceptance may be found to be sufficiently reliable if it is based on a sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field. The evidence of such scientific knowledge must be proffered by an expert who is sufficiently qualified by education, knowledge, training, and experience in the specific field of science.

[*Id.* at 449, 593 A.2d 733.]

Accordingly, *Rubanick* changed the emphasis for the admission of expert testimony from general acceptance in the scientific community to the methodology and reasoning supporting the testimony. *See* *Landrigan*, 127 *N.J.* at 404, 605 A.2d 1079.

Less than a year after *Rubanick*, the New Jersey Supreme Court was again presented with the question of admissibility of scientific evidence on the issue of causation in *Landrigan*, 127 *N.J* at 404, 605 A.2d 1079. The *Landrigan* trial court had ruled that an epidemiologist who had never examined the plaintiff and was not a physician, was not qualified to render an opinion that asbestos exposure caused colon cancer in a specific individual.

The New Jersey Supreme Court reversed. In it's decision, the Court stated:

[E]pidemiologists, like experts generally, must be able to identify the factual bases for their conclusions, explain their methodology, and demonstrate that both the factual bases and the methodology are scientifically reliable. That explanation will enable the trial court to determine whether the expert's opinion "will assist the trier of fact to understand the evidence or determine a fact in issue," Evid. R. 56(2), or whether the opinion is, in current parlance, "junk science."

**24* [*Landrigan*, 127 *N.J.* at 417] FN14

FN14. At no time was epidemiology required in a toxic tort case, but if such evidence was available and introduced it had to be evaluated under an objective, albeit more liberal standard than that used by the federal courts.

In *Landrigan*, the New Jersey Supreme Court explained that the trial court's role was to review proffered studies or other information to determine if they are of a kind normally relied upon by experts. Trial courts must also determine whether the opinions are derived from sound, well-founded methodology and supported by some expert consensus in the field. *Id.* at 417, 605 A.2d 1079. *See also* *Bahrle v. Exxon Corp.*, 279 *N.J.Super.* 5, 652 A.2d 178 (App.Div.1995)(excluding testimony by chemistry professor as to results of his experiments when professor failed to show that methodology was scientifically reliable under any relevant test.)

Recently, the New Jersey Supreme Court, expanded the federal court's less stringent admissibility standard as set forth in *Rubanick.* There the court recognized that the "obstacles plaintiffs generally confront concerning reasonable but unconfirmed theories of medical causation were not confined to toxic tort litigation." It ruled that the more relaxed *Rubanick* standard should be applied whenever a "medical cause-effect relationship has not been confirmed by the scientific community but compelling evidence nevertheless suggests that such a relationship exists." *Kemp*, 174 *N.J.* at 430, 809 A.2d 77. The court reasoned that the same concerns arise in those cases, as in toxic tort litigation, that a plaintiff might possibly be barred from recovery because a novel or relatively new scientific theory of causation has not as yet, satisfied the "extraordinarily high level of proof required in order to gain general acceptance in the scientific community." *Id .* Therefore, in New Jersey, scientific evidence is admissible in a civil case if "it derives from a reliable methodology supported by some expert consensus." *Suanez v. Egeland*, 353 *N.J.Super.* 191, 196, 801 A.2d 1186 (App.Div.2002). The party offering novel scientific evidence bears the burden of demonstrating its reliability. *Id.*

Reliability may be shown through: (1) the testimony of knowledgeable experts; (2) authoritative scientific literature; and (3) persuasive judicial decisions. *Suanez v. Egeland*, 353 *N.J.Super.* at 196, 801 A.2d 1186 (quoting *Windmere, Inc. v. International Ins. Co.*, 105 *N.J* . 373, 379, 522 A.2d 405 (1987)).

In *Suanez*, the court was presented with the issue of whether there was a scientific foundation for expert testimony by a biomechanical engineer that a low-impact automobile accident could not have caused plaintiff's herniated disc. *Id.* A court should not admit a purported scientific opinion "that is connected to existing data only by the *ipse dixit* of the expert." *Suanez*, 353 *N.J.Super.* at 201, 801 A.2d 1186 (quoting *General Elec. Co. v. Joiner*, 522 *U.S.* 136, 146 118 *S.Ct.* 512, 519, 139 *L.Ed.*2d 508, 519 (1997)). The defendant failed to establish the required foundation of reliability in any of these ways; nor did the defendant introduce into evidence any of the scientific literature upon which the expert relied. *Id.* Thus, finding no reliable scientific foundation for the proffered expert opinion, the court reversed the trial courts judgment for the defendant and remanded the case for a new trial on damages. *Id.*

***25** Finally, an expert opinion that fails to explain the causal connection between the act or incident complained of and the resultant injury or damage alleged, as well as opinions based on the expert's bare conclusions which are unsupported by factual evidence, are subject to the net opinion rule. Accordingly, such testimony is excluded. *Nguyen v. Tama*, 298 *N.J.Super.* 41, 688 A.2d 1103 (App.Div.1997); *Dawson v. Bunker Hill Plaza Assoc.*, 289 *N.J.Super.* 309, 673 A.2d 847 (App.Div.1996).

IV. DISCUSSION

A. Experts

1. Dr. Steven Levine

Dr. Levine is a highly qualified neurologist who specializes in stroke. His education, experience and training focus on stroke. There is no dispute that Dr. Levine is qualified as an expert in the field of neurology. The only question before the court is whether Dr. Levine's opinion that PPA can cause stroke satisfies the *Kemp* requirements. The court will now address the reliability of Dr. Levine's opinion.

a. Expertise

Dr. Levine is a board certified neurologist and is a Professor of Neurology and Director of Cerebrovascular Education at The Mount Sinai School of Medicine and Medical Center in New York City. He was previously the Detroit area principal investigator for the National Institute of Health and served as the co-chair of both the Michigan stroke Initiative and the America stroke Association Operation Stroke Detroit. Dr. Levine has also treated numerous patients who have had strokes during his medical career.

b. Peer Review and Publication

Dr. Levine has published his opinions that sympathomimetic drugs, including PPA, can cause strokes. Dr. Levine's first published opinion about sympathomimetics, including PPA, was published in the early 1990s.

c. Acceptance within the Scientific Community

Dr. Levine testified that he and other neurologists agree that PPA can cause stroke. Although his opinion may not have attained general acceptance within the medical community, there is some consensus within the medical community that PPA can cause stroke.

Q Do you hold that opinion to a reasonable degree of medical certainty?

A I do.

Q And do you know that all of [the following] stroke neurologists-Doctors Lou Caplan, in Boston; Ed Feldmann, at Brown, Providence, Rhode Island; Carlos Kase at Boston University; John Brust at Columbia, and Mike Sloan, at Rush in Chicago-agree with you that PPA can cause ischemic stroke?

A Yes.

Just as being the only neurologist to believe PPA can cause stroke might undermine that Dr. Levine's opinion, the support of other knowledgeable stroke neurologists reinforces the reliability of Dr. Levine's testimony.

d. Authoritative Scientific Evidence

Dr. Levine, in reaching his conclusions regarding PPA relied upon the kinds of facts and data that stroke neurologists rely on in the course of their academic and clinical work. Dr. Levine highlighted the evidence that he relied upon in reaching his opinion. Dr. Levine explained,

***26** So there are about 10 kinds of evidence that sort of, if you will, all converge or point to one direction with regard to supporting ⋯ my opinion that PPA in select individuals can cause an infarct. These lines of evidence are case reports that are published that are peer reviewed in the medical literature. Short series, two cases that are included in that, adverse events, adverse drug reports that were reported to the FDA. Animal studies with sympathomimetics. Chemical structure, function, and pharmacological class that are similar with PPA to amphetamines and ephedrine. And there's some analogy as well to naturally occurring conditions that altered sympathetic tone, where there's a disruption of the sympathetic nervous system⋯⋯ There's literature on similar drugs of the same class that have the same mechanisms of action. Similar mechanisms of action. There's biological plausibility based on a class of drug. The fact that PPA has a narrow therapeutic index. Human blood pressure experiments. Multiple textbooks. And in fact not just my personal experience, but also other stroke neurologists around the country's personal experience as well.

This scientific literature and scientific evidence, as Dr. Levine testified, is the same evidence that stroke neurologists rely upon everyday. The court finds this literature and evidence to be authoritative.

e. Methodology

Dr. Levine, when reviewing the scientific literature and evidence, focused on the science of cause and effect. He used sound methodology to reach his conclusion that PPA can cause stroke. Dr. Levine focused on biological plausibility, temporal association pharmacology, and dose-response relationship in reaching his conclusions.

Dr. Levine concluded that, "given that sympathomimetics are known to be a vasoconstrictor and affect cerebral vessels, then I think there is biological plausibility in the tenet that PPA can cause ischemic stroke, fits well and nicely within biological plausibility." Dr. Levine also testified that, "If you look at the reports and personal experience, and textbooks, at the epidemiological studies, there is a temporal

association with the medication, or the drug, and the effect. And also dose response, where higher doses are more likely to cause adverse events in question." In reaching this conclusion, Dr. Levine focused on PPA's ability to constrict the vessels and reduce blood flow.

Dr. Levine also recognized that sympathomimetic drugs vary in some significant ways, in particular, potency.

Q And you would agree, of course, Doctor, that the effects of PPA are not identical to the effects of cocaine?

A I think that they're not the same drug, but they have similar effects in terms of some of their pharmacology. They both can raise blood pressure. They both can vasoconstrict. Cocaine is much more [central nervous system] active than PPA is. So, yes, they're different drugs. Cocaine is on a potency level much more potent than PPA is, but they do share similar pharmacological effects, because they have similar sympathomimetic action.

f. Persuasive Judicial Decision

*27 This court is also aware that the Honorable Barbara Rothstein, United States District Court, Western District of Washington at Seattle, following a rigorous *Daubert* analysis, found Dr. Levine's testimony reliable scientific knowledge pursuant to Federal Rules of Evidence 702 and 703. The federal court determined that Dr. Levine's testimony is reliable scientific knowledge after considering the four *Daubert* factors: (1) whether the theory has been tested; (2) whether it has been subjected to peer review and publication; (3) its known or potential rate of error along with the existence and maintenance of standards controlling the technique's operation; and (4) the degree of acceptance within the scientific community. *Daubert*, 113 *S.Ct.* at 2796-2797. After determining that Dr. Levine's testimony, under these factors, was reliable, the federal court then determined that Dr. Levine's conclusions fit the situation at hand and were reached through a sound methodology. The federal court's decision is extremely persuasive given that the *Daubert* standard is more stringent than the *Kemp* standard and since the exact same issue, i.e., the admissibility of Dr. Levine's testimony that PPA can cause stroke, is before this court.

g. Conclusion

Dr. Levine has advanced several lines of evidence that suggest the probability of PPA causing stroke in some people. These lines of evidence focus on the Bradford Hill factors considered when assessing causality, e.g., temporality, congruence, consistency, and biological plausibility, and, as a result, bolster Dr. Levine's testimony. Dr. Levine relies upon the HSP, medical literature, case reports, and other evidence to support his conclusion that PPA can cause stroke in some people. Accordingly, this court, like the federal court, finds the substantial body of scientific evidence offered by Dr. Levine provides a sufficient basis to support his expert testimony related to PPA and stroke.

Therefore, the testimony of Dr. Steven Levine is admissible. The court finds that Dr. Levine's testimony is relevant and will assist the trier of fact to understand the relationship between PPA and stroke. The court also finds that Dr. Levine's reasoning and methodology are scientifically valid. Dr. Levine, like any other expert witness, may be cross-examined during trial to distinguish the evidence that he relies upon in forming his conclusion in the scientific literature from the facts in a given trial. Defendants own experts may also offer opinions that challenge Dr. Levine's conclusions. Thus, creating questions for the jury to weigh, and ultimately, resolve.

2. Dr. Paul M. Wax

Dr. Wax is a highly qualified medical toxicologist and emergency medicine specialist. His education, experience and training focus on toxicology and the effects of drugs and chemicals on people. There is no dispute that Dr. Wax is qualified as an expert in the field of clinical toxicology. The only question before the court is whether Dr. Wax's opinion that PPA can cause stroke satisfies the *Kemp* requirements. The court will now address the reliability of Dr. Wax's opinion.

a. Expertise

***28** Dr. Wax is one of only 300 medical toxicologists in the United States. In addition to this rare specialty, he is also an emergency medicine specialist. He did training in both fields and is board certified in both emergency medicine and toxicology.

As a medical toxicologist, Dr. Wax cares for patients who have been exposed to drugs and chemicals. He then attempts to sort out the possible clinical manifestation, the exposure, and attempts to manage the ill effects and prevent future exposure by reducing hazards and limiting exposure.

Dr. Wax held a teaching position at the University of Rochester where he taught residents and medical students about toxicology and poisoning and drug effects and drug interactions. During his tenure at the University of Rochester and Strong Memorial Hospital, Dr. Wax treated patients whom he believed had been injured by PPA.

Dr. Wax is also active on several editorial boards that discuss and develop clinical toxicology. For example, Dr. Wax is on the editorial board of the Journal of Toxicology, Clinical Toxicology, which is the official journal of the American Academy of Clinical Toxicology, one of the essential journals to our specialty. He is also on the Internet Journal of Medical Toxicology.

b. Peer Review and Publication

Dr. Wax has published numerous medical articles and chapters, including more than 30 journal articles in peer review literature, dozens of chapters in a variety of textbooks, and between 35 and 40 abstracts that have been published in a variety of journals. Dr. Wax has authored several articles and textbook chapters that consider the toxic effects of PPA and the drug's ability to cause significant vasoconstriction and hypertension.

c. Acceptance within the Scientific Community

Dr. Wax testified that, he holds his opinion that PPA can cause hemorrhagic and certain types of ischemic stroke to a reasonable degree of medical certainty.

Q First with regard to PPA causing hemorrhagic stroke and vessel constriction, vasculopathy, can you tell the court what your opinions are on that point?

A My opinions are that PPA can cause hemorrhagic stroke through different mechanisms, including vessel constriction, vasculopathy and hypertension.

Q Can you explain what vessel constriction is?

A Vessel constriction refers to a narrowing of the blood vessel, typically in the brain.

Dr. Wax testified that his opinion that PPA can cause stroke and certain types of ischemic stroke is recognized in the medical community.

Q Is it recognized in the toxicology community that there is a drug-induced vasculitis;

that vasculitis can occur from drugs?

A There is an extensive literature and it is in drugs-there is more literature in [other sympathomimetic drugs].

d. Authoritative Scientific Evidence

Dr. Wax discussed clinical evidence and scientific literature that support his conclusion that PPA can cause stroke. First, Dr. Wax explained that sometimes the appearance of vasculitis or vasculopathy can look quite similar to the appearance of vasospasm or vasoconstriction, evidenced by beading, which is descriptive of areas of narrowing vasoconstriction with other areas of a balloon dilatation of the blood vessels. Dr. Wax noted that beading is a concern from a hemorrhagic stroke standpoint because the areas of ballooning may indicate a weakening of the vascular endothecium integrity. He testified, "It would be a source of weakness that may burst or rupture and cause a bleeding, which in this case would be a hemorrhagic stroke."

***29** Dr. Wax also explained why he believes, based upon vasoconstriction, that PPA can cause ischemic stroke. Dr. Wax testified, "You clearly need good blood flow to supply the brain. If you don't get enough blood flow, this can cause a stroke as well and with vasospasm, if there is a reduced blood flow, if the brain is not getting adequate blood supply, this will also result in a stroke····"

Dr. Wax also discussed the types of data that he and other toxicologists and clinical practitioners rely upon. He noted that epidemiological evidence is considered, if it exists. Dr. Wax added that toxicologists and clinical practitioners also rely on case series, case reports, operations, retrospective reviews, perspective studies, clinical studies, and animal studies. Regarding the use of animal studies, Dr. Wax said,

Realizing that humans are not rats or mice, but there is some relationship and if there is a problem in rats or mice, there may be a similar problem in humans. I would never rely on that by itself because that may not pan out, but with other pieces of information that might be supportive data.

Dr. Wax relies heavily upon chemical structure analogy. Dr. Wax remarked,

Chemical structures ultimately dictate the function of the chemical or the drug, but drugs that are similar to one another, there tends to be a continuum of an effect. It is usually not yes or no. It may be more or less. And these drugs cause a number of different effects as well, so if there are 10 different effects you are looking at by the drug, some effects may vary and some effects may be very similar. You will see in textbooks and papers, tables which are comparing the types of effects of these different drugs that belong to the same family, such as the sympathomimetic drugs. Certain drugs may cause more vasoconstriction. Certain drugs may cause more CNS stimulation.

Dr. Wax also added that toxicologists and clinical practitioners rely on their own experience and expertise. He noted that physicians mature and develop their own fund of knowledge, which may not be in the literature, but based on their observations and experiences, adds to this decision making process.

e. Methodology

Much of this thought process or this methodology can be understood using certain published criteria that have been distributed in the past such as Bradford Hill for instance. Dr. Wax also considered the Bradford Hill criteria and the congruence of the scientific evidence when reaching his conclusions regarding PPA.

That's why, in my mind, the PPA is so striking because, for instance, there are all of these reports of stroke with PPA. You don't find a whole cadre of reports of hepatitis with

PPA or cancer with PPA. It is specific to these neurological problems to a large degree in terms of what we are discussing today and particularly hemorrhagic strokes. There is this specificity.

Dr. Wax also discussed temporality. He noted,

There is an exposure and there is an outcome. We need to make sure that if the exposure causes the outcome, the exposure needs to come before the outcome. But the outcome is important in terms of what are you defining as your outcome. An outcome is not necessarily a sentinel event, a warning event. It is the cerebral hemorrhage. That would be an outcome.

***30** Dr. Wax also discussed PPA's dose-response relationship.

In PPA literature we have problems with therapeutic dosing. We also have problems with overdose. I don't think anyone would argue that the vast majority of people most likely took this at therapeutic doses. Just a small minority took overdoses. Yet we have a lot of cases of severe toxicity with overdose. In terms of the ⋯ dose response, as we increase the dose, the likelihood of the problem goes up because the denominator certainly has gone way down in terms of the numbers of people who overdose. The [dose-response] is important.

And, again noting the importance of chemical structure analogy, Dr. Wax discussed the similarities between PPA and other closely related drugs like amphetamines and methamphetamines. Dr. Wax stated,

We can't ignore that [analogy] here. These other drugs, there is similar clinical literature, there is more animal literature like the amphetamine-induced vasculitis that strengthens this concern that there is an analogist findings.

Dr. Wax then considered the coherence of the totality of the scientific evidence and biological plausibility. Dr. Wax testified,

Biologically we are concerned about the vasoconstriction. We are concerned with hypertension, the development of stroke. In patients with chronic hypertension, that's the most common reason to have a cerebral hemorrhage. It is very plausible. It fits together. I put these things all together when I came up with my methodology.

f. Persuasive Judicial Decision

This court is also aware that the Honorable Barbara Rothstein, United States District Court, Western District of Washington at Seattle, found the testimony of similar toxicologists, who relied upon the same types of evidence, and who used the same methodology reliable scientific evidence under *Daubert. Id.* After determining that their toxicological testimony was reliable, the federal court then determined that this testimony was relevant and was reached through a sound methodology. Again, the federal court's decision is extremely persuasive given that the *Daubert* standard is more stringent than the *Kemp* standard and since the exact same issue, i.e., the admissibility of testimony that PPA can cause stroke, is before this court.

g. Conclusion

The testimony of Dr. Paul M. Wax is admissible. The court finds that Dr. Wax's testimony is relevant and will assist the trier of fact to understand the relationship between PPA and stroke. In particular, Dr. Wax's testimony regarding vasoconstriction, the mechanism of action, biological plausibility, and analogy to other sympathomimetics amines will assist the trier of fact to understand how PPA effects the body. Dr. Wax's testimony that PPA can cause both hemorrhagic and ischemic stroke is also admissible.

In reaching his conclusions, Dr. Wax relies upon the types of evidence and the methodology that experts in the medical and toxicological communities generally use. The court will also allow Dr. Wax to extrapolate from one subpopulation to another so long as he has an objective basis for doing so.

3. The Remaining Causation Experts

*31 For the reasons previously stated, this court will also admit expert testimony from Dr. Jerome Avorn, Dr. Robert A. Egan, Dr. Edward Feldman, Dr. Steven J. Kittner, Dr. Raymond Lake, Dr. James McDowell, Dr. Walter J. Molofsky, Dr. Paul Pentel, Dr. George Ricuarte, Dr. Stanley Tuhrim, Dr. Alan Woolf, and Dr. Gary Zaloga that PPA can cause stroke. These experts are all highly educated and experienced, rely upon the same scientific evidence and sound methodology used by Drs. Levine and Wax to conclude that PPA can cause stroke.

This court, as previously stated, is aware of the federal court's order finding the testimony of these doctors reliable and relevant and concluding that their opinions were reached through a sound methodology. As stated previously, the federal court's decision is extremely persuasive because the *Daubert* standard is more stringent than the *Kemp* standard and since the exact same issue, i.e., the admissibility of testimony that PPA can cause stroke, is before both courts. Clearly, their testimony must meet the more liberal *Kemp* standard since it has already satisfied the *Daubert* criteria for admissibility. Thus, this court will admit testimony that PPA can cause hemorrhagic and ischemic stroke from these experts.

4. Dr. W. Steven Pray

The defendants' remaining expert challenge involves Dr. W. Steven Pray is not being offered as a causation expert. Accordingly, it is premature for the court to address the admissibility of his expert testimony. The court will consider the admissibility of Dr. Pray's testimony when, and if, Dr. Pray is asked to testify at trial in a given case.

B. Proofs

1. Methodology and Evidence Used

This court must only admit testimony from the plaintiffs' expert that has a scientifically reasonable factual basis and a sound methodology. *Landrigan*, 127 N.J. at 417, 605 A.2d 1079. "The courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rider v. Sandoz Pharm. Corp.*, 295 *F.*3d 1194, 1202 (11 Cir.2002)(quoting *Rosen v. Ciba-Geigy Corp.*, 78 *F.*3d 316, 319 (7 Cir.1996)). After exhaustively reviewing the methodology employed by the plaintiffs' experts and carefully evaluating the level of acceptance of the bases for their claims that PPA is capable of causing stroke in humans, this court concludes that the plaintiffs' experts are permitted to testify. The court finds that these experts used the same methodologies that are used in hospitals across the country, taught at medical schools, and described in medical textbooks. Moreover, the evidence relied upon by the plaintiffs' experts consists of the type of scientific evidence that is ordinarily relied upon within the medical and scientific community when considering causation.

2. Epidemiological Evidence

The court has considered the defendants' contentions, and the plaintiffs' responses, regarding the quality of the HSP design and the power and significance of the HSP results. The court has also evaluated the study and has considered the extent that

defendants' alleged "flaws" compromised the study. This court is not persuaded by the defendants' arguments, however, especially given that the FDA has accepted the HSP and two highly respected, peer-reviewed scientific journals. The court finds the HSP to be a well-conducted epidemiological study and reliable evidence that PPA can cause stroke. The interpretation of the HSP is a task for qualified experts as is the application of the HSP results to a particular case. *See* *Grassis v. Johns-Manville Corp.*, 248 *N.J.Super.* 446, 591 A.2d 671 (App.Div.1991). Consequently, this court will admit the HSP and will allow the experts to interpret the HSP design and its results and render opinions based on the HSP.

***32** The HSP dramatically strengthens the plaintiffs' argument that their expert testimony of causation be admitted because it supports and complements other scientific knowledge, e.g., animal studies, case reports, biological plausibility, and analogy to similar chemicals. For that reason, the court also finds that other non-epidemiological evidence offered by the plaintiffs' experts that complements the HSP findings is admissible.

3. Extrapolation

The HSP made valid findings as to some specific subpopulations and those findings can be extrapolated to other subpopulations so long as the expert has an objective basis for doing so. Study results are often extrapolated to other subpopulations for a variety of reasons. For example, it may be unethical for the pharmaceutical industry to expose young children to drugs during clinical trials. Likewise, extrapolation between the genders is frequently performed in the medical community. Obviously, extrapolation presents problems, but these problems do not render extrapolation scientifically unreliable. The court finds extrapolating evidence from one age group or gender to another sufficiently reliable and will allow experts to extrapolate evidence so long as the expert has an objective basis. However, extrapolation cannot be scientifically justified as to those individuals who last ingested PPA more than three days before the onset of their stroke because of significant temporality concerns.

C. Analysis of Injury Types Allowed And Excluded

Plaintiffs also put forward claims that PPA can cause cardiac and central nervous system injuries. Plaintiffs offer limited support for their experts' testimony of the purported association between PPA and cardiac and central nervous system injuries, e.g., seizures and psychoses. Since 1990, only one case report concluding that PPA can cause cardiac injury has been published. C. Chin et al., *Cardiomyopathy Induced by Phenylpropanolamine,* 123 J. Pediatrics 825, 827 (1993). No epidemiological studies have considered the association between PPA ingestion and these injuries. The court finds that the totality of evidence available does not provide enough support for plaintiffs' expert testimony that PPA can cause central nervous system injuries. The court is uncertain, given the present record, whether the totality of the evidence supports expert testimony that PPA can cause cardiac injury through hypertension or vasoconstriction. However, given the existing animal data, clinical trials, and other lines of evidence, the court will conduct a Rule 104 hearing to review and evaluate the claim that PPA can cause cardiac injuries through vasoconstriction or hypertension, if necessary, during trial.

V. CONCLUSION

After examining the parties' briefs and exhibits and for the reasons explained above, the court hereby grants the defendants' motion to preclude the plaintiffs' experts' opinions in part. The plaintiffs' experts' opinions that PPA is capable of causing stroke in men and women are admissible. The court will conduct a Rule 104 hearing to consider the admissibility of testimony that PPA is capable of causing cardiac injury during trial if

necessary. The plaintiffs' experts may not offer testimony that PPA is capable of causing seizures or other injuries. Finally, the admissibility of testimony from Dr. Pray is denied without prejudice. The court will conduct a Rule 104 hearing to consider the admissibility of Dr. Pray's testimony during trial if necessary.

In re Phenylpropanolamine (PPA)
Not Reported in A.2d, 2003 WL 22417238 (N.J.Super.L.)

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