EXPERT REPORT OF

RICHARD A. PARENT, PHD, DABT, FATS, RAC, ERT

IN THE MATTER OF

[redacted]

VS.

[redacted]

IN THE

UNITED STATES DISTRICT COURT

[redacted]

CASE NO. [redacted]

CONSULTOX, LIMITED

DAMARISCOTTA, MAINE

FEBRUARY 27, 2004

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QUALIFICATIONS

I, Richard A. Parent, PhD, DABT, FATS, RAC, ERT, am a board certified toxicologist with over 12 years' experience in the field of industrial toxicology and an additional 20 years' experience in litigation support for both the plaintiff and defense. I have testified in local and federal courts as an expert in toxicology and have given expert testimony in the disciplines of toxicology and chemistry. During my career, I have spent 10 years in research on organic chemicals at American Cyanamid Company. In the field of toxicology, I have initiated and carried out an active program in product safety relating to toxicology for the Xerox Corporation. I have directed two contract toxicology laboratories: Food and Drug Research Laboratories, Inc. and Gulf South Research Institute, Life Sciences Division. In 1984, I established Consultox, Limited, a toxicology consulting firm, and have since consulted in product safety for various industries and have designed toxicology studies to assess the safety of materials being considered for use in various products. For litigants, I have provided toxicological support and have addressed causation issues for the plaintiff as well as the defense. I am board certified by the American Board of Toxicology, the Academy of Toxicological Sciences, and the Regulatory Affairs Professional Society. I am a recognized expert in toxicology in France and the European community. I present myself to the Court as an expert in the fields of toxicology and chemistry. For the Court's information, I offer my curriculum vitae in Appendix A and a listing of my testimony in past depositions and trials in Appendix B.

MATERIALS REVIEWED

- Medical Records of Ms. [redacted] dating from April 17, 1998, to October 28, 2002 (See Appendix D).
- Excerpts of Ms. [redacted] depositions of May 21, 2003, and October 21, 2003.
- Letter Report of Malcolm H. Gottesman, MD, to Curyl Weiner dated January 27, 2004 (See Appendix D).
- Letter Report of Lawrence W. Shields, MD, to Weiner & Cox dated December 15, 2003 (See Appendix D).
- Food and Drug Administration, Center for Applied Nutrition and Food Safety, Office of Special Nutritionals, Adverse Effects Files On Ephedrine Alkaloid-containing Dietary Supplements from June 1, 1997, to March 31, 1999.
- Peer-reviewed literature as cited in this report.

INTRODUCTION

It is my understanding that Ms. [redacted] at the time of the pertinent incident, was a 44-year-old woman with a 20 pk-yr smoking history having quit in 1991, no alcohol

consumption of significance and regular use of caffeine in both tea and coffee. Furthermore, I understand that neither she nor her family demonstrated any prior history of either stroke or seizures, but she did have a history of sinus headaches. On or about 1537 hours on November 21, 2000, Ms. [redacted] was found on the restroom floor of her workplace in a state of lethargy with uncontrolled shaking. At that time, she described a severe headache localized to the right side of her face extending down to her neck with flaccid paralysis of the left arm and leg. She was described as having had a stroke.

In her deposition and elsewhere, Ms. [redacted] describes having taken six Metab-O-LITE™ pills per day for up to two weeks prior to her stroke. The Metab-O-LITE™ label indicates that each pill contains about 12 milligrams of Ephedra, also known as "ma huang", and Ms. [redacted] urine screen was consistent with this dosing regimen since she tested positive for amphetamines. Ephedra alkaloids are considered in a class with amphetamines and produce positive urine toxicology screen tests for amphetamines.

During her hospital stay after her stroke, Ms. [redacted] was examined and found to have had an acute cerebrovascular accident of her right carotid artery with CT scan showing a large area of infarct in the region of the right mid-cerebral artery. The impression of the attending physician was an acute thrombotic cerebrovascular accident and yet thrombotic factors were found to be negative. Dr. Menawat suggested that the acute cererbrovascular accident was likely caused by occlusion of the right carotid artery from a plaque rupture. After some diagnostic testing, Dr. Anouti at the Henry Ford Hospital later agreed that "she had experienced some plaque rupture or perhaps carotid dissection".

Subsequent to her hospital stays, Ms. [redacted] began experiencing seizures as noted by Dr. Posadas on February 26, 2001, and Dr. Mangalick on the following day. The latter suggested that the seizures were secondary to the stroke mentioned above and sent a letter to Dr. Posadas on March 26, 2001, describing a second seizure. Subsequent seizures were noted on April 10, 2001, by Dr. Weiss, 2-3 more seizures noted on April 23, 2001, and a total of five seizures noted by Dr. Leuchter after Ms. [redacted] visit of May 1, 2001. Dr. Leuchter clearly identifies her prior stroke as being a cause of these seizures. Additional seizures are noted by Dr. Leuchter, and he describes Ms. [redacted] condition as "chronic seizure disorder as well as stroke". See Appendix D for a more complete summary of Ms. [redacted] medical records.

I will begin my report with some brief background information on the ephedra alkaloids

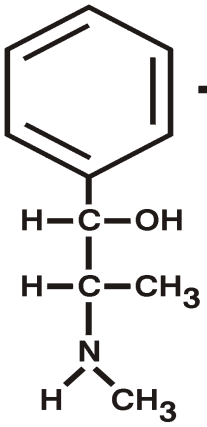
and their mode of action followed by a considerable discussion about the known adverse-effects of ephedra alkaloids published in the peer-reviewed literature and in Adverse Effect Reports (AERs) of the Food and Drug Administration. I will then address a formal causation analysis using the Hill Criteria to establish a causal connec-tion between Ms. [redacted]' stroke and subsequent seizures as well as her exposure to ephedra alkaloids from the Metab-O-LITE™ diet formulation that she had been taking at the time of her stroke.

THE EPHEDRA ALKALOIDS

It should be understood that the ephedra alkaloids are based on the first two chemical structures (Figures I & II) indicated below. I also have chosen to add additional chemical structures for methamphetamine (Figure III) and amphetamine (Figure IV) in order to demonstrate the striking similarity between the ephedra alkaloids and the amphetamines.[1] It is not surprising then that both the ephedra alkaloids (I & II) and the amphetamines (Figures III & IV) act on alpha- and beta-adrenergic receptors producing similar signs and symptoms to the ephedra alkaloids shown below.[2] It also is not surprising that chronic use of ephedrine alkaloids has been thought to be addictive.[3]

AMPHETAMINE-LIKE COMPOUNDS

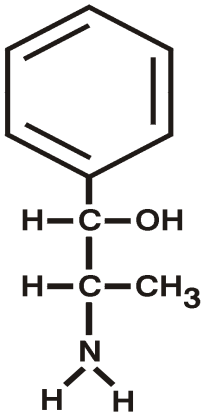
FIGURE I



Ephedrine
Pseudoephedrine

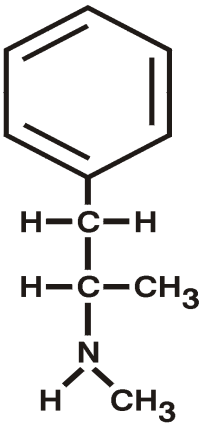
METABOLISM

FIGURE II



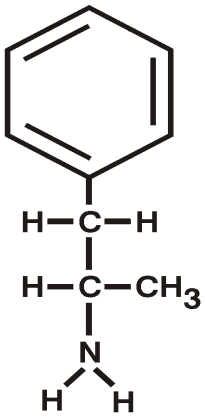
PPA (phenylpropanolamine)
Norephedrine
Norpseudoephedrine

FIGURE III



Methamphetamine

FIGURE IV



Amphetamine

Ephedra alkaloids from ma huang contain at least four active components bearing the structures indicated above: (–) ephedrine, (+) pseudoephedrine, (–) norephedrine, (+) norpseudoephedrine.[4] The latter two components are phenylpropanolamines (PPA). Since each of these two chemical structures contain two asymmetric centers, there are four possible optical isomers for Structure I (Figure 1) and four possible optical isomers for Structure II (Figure 2). In addition, we should note that the phenylpropanolamines

are metabolites of the corresponding ephedrine molecules. Thus, there are eight possible individual molecules which compromise what we consider to be ephedra alkaloids:[5] (–) ephedrine, (+) ephedrine, (–) pseudoephedrine, (+) pseudoephedrine, (–) norephedrine (PPA), (+) norephedrine (PPA), (–) cathene and (+) cathene.[6]

Ephedra alkaloids have been sold under the names "ma huang" or "*Ephedra sinica*"[3] and some of the formulations containing these alkaloid mixtures are sometimes referred to as "herbal fen-pen" and "herbal ecstasy".[7]

Adverse event reports from the FDA files have included hypertension, tremors, abnormal heart rhythms, seizures, psychoses, stroke, heart attacks and death.[8] As early as August 1998, many states restricted the use of ephedrine as a controlled substance[9], and on November 2, 2000, the U.S. Food and Drug Administration asked drug com-panies to stop marketing products containing the ephedra alkaloid and metabolite phenylpropanolamine (PPA) and that it was taking steps to see that the chemical was removed from all drug products.[10]

In consideration of the above discussion, our approach to evaluating the toxicity of ephedra alkaloids such as "ma huang" will include discussions of all isomers that are part of the class and that are present in the "ma huang" preparation of interest here including phenylpropanolamine.

ADVERSE EFFECTS OF EPHEDRA ALKALOIDS

It is appropriate to begin this discussion by quoting some of the authors who have studied and published on the ephedra alkaloids. Consider the following quotations: "Ephedrine appears to predispose to both ischemic and hemorrhagic stroke",[11] "Nutritional supplements containing *Ephedra sinica* (ma huang), a botanical source of ephedrine alkaloids have been linked to several episodes of ephedrine toxicity and at least 17 deaths . . .",[12] ". . . caffeine-phenylpropanolamine combinations increase the risk of stroke" - a 1991 report,[13] "This agent [PPA] can cause strokes and other significant sequelae of elevated blood pressure in susceptible individuals" - American Medical Association, 1991,[14] and in a 1987 report involving intracerebral hematoma "This report should alert physicians in general to this potentially fatal side effect of PPA, a commonly used over-the-counter drug".[15] Finally, in a definitive epidemiology study on phenylpropanolamine, the "Hemorrhagic Stroke Project", the following quote appears, "The results suggest that phenylpropanolamine in appetite suppressants and possibly in cough and cold remedies is an independent risk factor for hemorrhagic stroke in women".[16]

The "Hemorrhagic Stroke Project" (HSP) was a study carried out between December of 1994 and July of 1999 and involved the identification of 1,714 patients from 43 hospitals.[16] Patients were screened carefully for inclusion into the project with particular emphasis on elimination of confounding factors and inclusion of only those whose exposure window was deemed appropriate. Four hundred twenty-five patients with subarachnoid hemorrhages and 277 with intracerebral hemorrhages were chosen for this study. Others not eligible for inclusion were 389 patients who died within 30 days of the stroke and 194 patients who could not communicate as a result of their stroke. Exposure windows were clearly defined for both multiple dosing and for first dose of phenylpropanolamine containing dietary supplement or cold preparation. Using a control group of 1,376 patients for comparison, a statistically significant odds ratio of 16.58 was calculated for an association between use of appetite suppressants containing PPA and hemorrhagic stroke in women. The results of this study led the authors to conclude the following: "Our study provides strong epidemiological evidence of the association between the use of phenylpropanolamine and the risk of hemorrhagic stroke".[16]

Between 1969 and 1991 the FDA received 22 spontaneous reports of hemorrhagic stroke associated with phenylpropanolamine in appetite suppressants or cold medications (cited in Reference 16), while the Centers for Disease Control and Prevention (CDC) reported on 500 cases of adverse reactions to ephedrine-containing products in Texas from December of 1993 to September of 1995.[17,18] Reports of stroke, myocardial infarctions, chest pain, seizures, insomnia, nausea, vomiting, fatigue, dizziness and 8 fatalities were submitted to the CDC. In addition, the Texas Poison Control Network has received an additional 300 adverse reaction reports.[17,18] I have reviewed numerous other adverse reaction reports from the FDA files[4] including a separate file on Metabolife which included 29 cases of stroke, 22 myocardial infarctions, 3 cardiac arrests, 2 brain hemorrhages and 46 seizures.

There are numerous case reports of various types of adverse reactions to the ephedra alkaloids including elevated blood pressures,[19-30] psychoses,[7,31-45] seizures,[17,18,21,39,46-49] cardiac effects,[50-59] hemorrhagic stroke,[11,15,21,39,60-76] ischemic stroke[11,39,71,78-84] and death.[16,21,65,85,86] One study involving the review of 140 cases of adverse events related to ephedrine use in dietary supplements included 17 cases of elevated blood pressures, 13 cases of tachycardia or palpitations, 10 stroke cases, and 7 seizures. This report was based on FDA Adverse Events dating from June 1, 1997, to March 31, 1999.[86] Another report from the FDA files describes 24 cases of intracranial hemorrhages, eight seizures or hypertensive encephalopathy and eight deaths mostly due to stroke related to PPA use.[39]

It appears clear that the potential for a causal link between ephedra alkaloids and stroke may be significant. Further, it also would appear that seizures would be considered an expected sequelae following a cerebrovascular accident (CVA). Now we will consider the formalization of this causal connection using the criteria of Sir Bradford Hill[87]. Above we have presented a solid foundation for considering all of the ephedra alkaloids as a class of compounds capable of producing stroke and seizures. In addition, we have indicated that phenylpropanolamine is not only a component of ma huang, but it is a well established metabolite of ephedrine. Since Ms. [redacted]' exposure was to an ephedra mixture called "ma huang" containing both ephedrine and phenylpropa-nolamine (PPA) and since PPA is metabolite of ephedrine, we consider it justifiable to address the toxicology of the ephedra alkaloids together.

CAUSATION - THE HILL CRITERIA

A. B. Hill[87] describes criteria for establishing general causation. These criteria have been refined somewhat since his original paper but have not changed significantly. The Hill criteria are widely accepted, and the International Agency for Research on Cancer uses many of these criteria as part of their classification scheme for carcinogens. The Hill criteria apply to human studies and propose a set of requirements to be met in order to establish causation. Some of the criteria allow for the use of data from controlled animal studies in order to establish the target organs and mechanisms of action of particular toxicants. We will apply this criteria to the possible establishment of a causal connection between the ephedra alkaloids, including ephedrine and phenylpropa-nolamine, and stroke with secondary seizures as experienced by Ms. [redacted].

1. Strength of Association

The essence of this criteria involves an assessment of the extent to which a particular disease coincides with a particular exposure. The incidence of the disease does not have to be high in order to establish a strong association. In the case of a rare disease, the finding of even a few cases within a small population who have been treated with a particular drug would be of great significance.

Clearly, the strongest piece of evidence that there is an association between ephedra alkaloids and stroke is the study of 702 patients involved in the Hemorrhagic Stroke Project (HSP).[16] This highly controlled epi-demiology study reports a statistically significant odds ratio of 16.58 for stroke in women using dietary supplements containing phenylpropa-nolamine (PPA), and this study limited its investigation to hemorrhagic strokes only.

This study, by itself, would suffice to raise serious questions about the safety of ephedra alkaloids. Beyond this, there are numerous case studies which report both hemorrhagic [11,15,21,39,60-77] and ischemic strokes.[11,39,71,78-84] In addition, and pertinent to this case, there are numerous reports of seizures related to the use of amphetamine-like ephedra alkaloids.[17,18,21,39,46-49] I also have reviewed many other reports of adverse events not yet published in the open literature, and it is clear, again, that an association exists between use of ephedra alkaloids and stroke and seizures. One government report describes numerous cerebral vascular accidents and cases of seizures from Ephedra use including 29 stroke cases and 46 seizures from Metabolife alone.[4]

Ms. [redacted] suffered an ischemic stroke causing tissue damage to the vascular endothelium of the brain as a result of taking a dietary supplement, Metab-O-LITE™, containing ephedra alkaloids, coupled with her normal daily diet containing caffeine. Subsequent to her injury, she began having seizures which her physicians have indicated are secondary to her stroke.

It should be apparent from the published information cited above that the causal relationship between ephedra alkaloids and stroke is very strong, indeed. The HSP results alone are a serious indictment of the safety of phenylpropanolamine (PPA), one of the ephedra alkaloids and a metabolite of ephedrine. It should be noted that the dietary aid taken by Ms. [redacted] contained "ma huang" which, in turn, contains ephedrine and PPA.

2. Consistency of Association

Hill[87] asks the question, "Has it been repeatedly observed by different persons, in different circumstance and times?". In other words, have similar findings been observed by different observers.

The combination of events that have been described as a result of ingestion of ephedra alkaloids are consistent with the resulting diseased state. Consider the fact that these alkaloids cause a significant increase in blood pressure in man[19-30,88-92] and in animals.[90,93-96] There is a consistency in the findings reported in the literature related to this response to ephedra alkaloids. It is also this hypertensive response which gives rise to the rupture of weakened blood vessels and ischemia resulting from dislodgement of plaque from the vessel walls. Thus, the consistency

reported regarding blood pressure elevation with amphetamine-like substances such as the ephedra alkaloids even in healthy subjects must be noted. Those who are susceptible to these vascular problems then experience the stroke syndromes that we have described. This finding coupled with the consistent reports from numerous different investigators from different laboratories and clinics adds emphasis to the consistency of causal association between ephedra alkaloids and stroke.

The peer-reviewed literature is replete with reports of both hemorrhagic and ischemic strokes related to PPA[16,22-30,39,71,82,83], ephedrine[11,60,86], pseudoephedrine[52], "ma huang"[16,78,80] and combinations of ephedra alkaloids and caffeine[21,78]. In addition, cerebral vascular accidents have been reported from the use of both dietary supplements[15-18,64,67-75] and cough preparations[16-18,76,84]. The consistent ingredients in all of these reports are ephedra alkaloids, and the response to these alkaloids is consistently similar.

Ms. [redacted] clearly fits into a consistent pattern regarding her reaction to the ephedra alkaloids in her Metab-O-LITE™ dietary supplement. She took the supplement for a couple of weeks prior to the stroke and even took at least two pills on the morning of her stroke. Her response was classic but did not involve an obvious extended hypertensive event. In the absence of alternative causes as described by both Drs. Shields and Gottesman, Ms. [redacted] pathological sequelae is clearly consistent with a transient hypertensive response and resulting ischemic stroke and tissue damage. Several seizures followed. The pattern is consistent with events described in the literature related to ephedra alkaloid toxicity.

3. Specificity of Association

The specificity of an association describes the precision with which the occurrence of one variable will predict the occurrence of another. This criterion overlaps the strength of association to some extent but focuses more on the direct link between a specific disease and a specific cause for that disease. When dealing with human populations, this specificity is rare.

Having dismissed alternative causes for the type of stroke under consideration herein, it may be worthwhile to look at specific cases which bear similarity to the situation of interest, that is, a large infarct in

Ms. [redacted]' right mid-cerebral artery. While we have listed above the numerous examples of ischemic events resulting in stroke,[11,39,71,78-82,84] consider the descriptions of the cases that follow: a left middle-cerebral artery infarction after use of a combination of ma huang and caffeine in a person with no vascular or thrombolytic risk factors;[78] a 33-year-old woman hospitalized for cerebral infarction on the left side from use of ma huang;[80] a case report involving a thalamic infarction after taking ephedrine;[11] three cases of PPA ingestion resulting in hypertensive encephalopathy indicative of stroke without hemorrhage;[39] two cases of ischemic infarct in the middle-cerebral artery suggesting necrotizing angiitis, vascular spasms, and a hypertensive incident;[82] two cases of cerebral infarction following prolonged use of PPA;[71] a cerebral infarction after taking PPA the previous evening;[83] two additional cases of cerebral infarction after using PPA,[71] and a case of accelerated hypertension resulting in a cerebral infarction with permanent right-sided hemiplegia as a result of a PPA-containing cold medication.[84]

While I have only described a few of the case reports cited in the literature and virtually none of the hundreds of reports cited in the FDA's Adverse Drug Reaction files, it should be clear that Ms. [redacted] medical sequelae has been experienced by many who have used the ephedra alkaloids in various preparations. It also should be clear that there is a consistency in the resulting pathogenesis.

4. Temporality

Hill[87] asks "Which is the cart and which is the horse?" If a disease state exists prior to exposure to a medication, the exposure may exacerbate the disease but may not have caused the disease. The appearance of a diseased state must follow treatment with the medication being addressed.

It appears clear that Ms. [redacted] was void of any pre-existing risk factors for stroke, and there is no familial history to suggest the existence of such risk factors.

There is little question that Ms. [redacted] took the Metab-O-LITE™ dietary supplement. According to her own testimony, she consumed two Metab-O-LITE™ tablets three times per day. She testified in her deposition that she had taken two pills containing 12 mgs "naturally occurring Ephedra" ("ephedrines") the morning of her stroke and that she was very regular in

her regimen. That would suggest that she also took two pills with her lunch as was her routine. This dosing scenario would meet the rigid requirements for inclusion in the Hemorrhagic Stroke Project and would therefore more than qualify according to the criteria set forth herein by Hill.[87]

5. Biological Gradient

Dose-response is the foundation of good toxicological studies. The higher the dose or the longer the treatment, the more severe the response or the more prevalent the response. Dose cannot only be expressed as a single dose producing an acute response, but also by specifying the daily dose and treatment period. The latter is more appropriate in this situation.

It is not always possible to measure increasing response with increasing dose of a drug depending on the response being measured. Usually dose-response experiments are carried out in animals where the experiment is highly controlled in every way possible. In the case of the ephedra alkaloids, there is data in both animals and in man. The Hemorrhagic Stroke Project reported an odds ratio of 2.3 for PPA doses of 75 mg and above but an odds ratio of 1.01 for those using lower dosages of PPA.[16] Three human studies used blood pressure as an endpoint. In one study of normotensive subjects were treated under controlled conditions to three different doses of PPA (25, 50, 100 mg). Blood pressure was increased in a dose-dependent manner in the two highest dosing levels.[97] A controlled double-blind randomized crossover study of 5 men and one woman also showed a significant dose-dependent increase in blood pressure with increasing doses of PPA.[30] Yet another study of 15 healthy males also showed dose-dependent increases in blood pressure relative to increasing doses of PPA.[98]

Animal studies also demonstrate this dose dependency. A controlled rat study reported a significant dose-dependent increase in myocardial necrosis relative to PPA dose.[99] Ephedrine-treated rabbit aortic strips and dog femoral strips produced dose-dependent contractions indicating a pressor response,[94] and rats treated with PPA or l-norephedrine demonstrated a dose-dependent increase in blood pressure.[96] Additional studies have been published pertaining to the dose-response relationship between ephedra alkaloids and pressor responses, but the studies cited should be enough to show that the dose-response relationship between ephedra alkaloids and pressor response is a reality.

Ms. [redacted] not only dosed with ephedra alkaloids on the morning of her stroke, but, considering her routine, she also most probably had caffeine in her system. Caffeine has been shown to interact with ephedra alkaloids producing an additive, if not synergistic, effect. Controlled human studies[90,100,101] have demonstrated this interaction, and animal studies have demonstrated dose-dependent behavioral changes when treated with combinations of caffeine and ephedra alkaloids.[102,103] One study in rats reported sub-arachnoid and cerebral hemorrhages in animals treated with caffeine in combination with PPA.[104]

Dose-dependency of the hypertensive response to ephedra alkaloids has been demonstrated in both animals and man. An additive or synergistic interaction with caffeine also can be supported by the cited peer-reviewed literature.

6. Plausibility and Coherence

I will consider these criteria together since they impinge on the same theme voiced by Hill[87] with regard to coherence ". . . the cause and effect interpretation of our data should not seriously conflict with generally known facts of the natural history or biology of the disease". In addition, hypotheses based on sound scientific principles should be presented to explain the phenomena under consideration and to demonstrate the plausibility of the causal conclusions being reached. It is desirable to provide experimental evidence to support the hypothesis, but this is not always available.

Ephedra alkaloids, as demonstrated above, produce dose-dependent increases in the pressor response of the cardiovascular system.[16,20,30,94,96-99] This response is accomplished by a combination of events resulting from the ephedra alkaloids having both alpha- and beta-adrenergic activity.[7,18,105-107] As with amphetamines, this increased pressor response is accomplished by stimulating these adrenergic receptors resulting in vasconstriction and cardiac stimulation which, in combination, results in increases in blood pressure.[7,18]

Stimulation of alpha-1-adrenergic receptors produces contraction of the vascular smooth muscle and increased contractile force of the heart, while stimulation of alpha-2 receptors results in decreased insulin secretion, platelet aggregation, and release of norepinephrine.[108] Norepinepherine is an agonist for alpha-receptors with little interaction with beta-receptors and is released from sympathetic neurons[2] upon stimulation by the

ephedra alkaloids; consequently, it too participates in the vasoconstriction process further enhancing the pressor response.[109]

The ephedra alkaloids produce a hypertensive response, that is logically related to cerebrovascular accidents resulting from weakened vasculature. Evidence of the pressor response is regularly reported as "beading" or "segmental constriction" of the vasculature[15,16,60,64,66]. We have shown above that the vasoconstrictive pressor response results from ephedra alkaloids acting on the adrenergic receptors. It is scientifically sound to consider these relationships based on the evidence available. Further, it also is scientifically logical to attribute both ischemic and hemorrhagic strokes to pressor effects on weakened vasculature and disrupted blood flow with resulting infarctions. The foundation for meeting this criteria has been firmly constructed above.

In Ms. [redacted]' case, she did not suffer a hemorrhagic stroke, but she did suffer an acute cerebrovascular accident (CVA) and a cerebral infarct resulting from a thrombolytic event or dislodgment of plaque. This resulted in disruption of flow and consequent endothelial cell death. Both Drs. Shields and Gottesman considered and dismissed alternative causes for the CVA. In addition, her medical records indicate that she had no obvious risk factors for clot formation. In his report, Dr. Shields points out the turbulence resulting from segmental vasoconstriction producing a situation favorable to plaque dislodgement and subsequent ischemia resulting from flow disruption.

What we know about Ms. [redacted] CVA is that she took a mixture of ephedra alkaloids which has been clearly demonstrated to cause significant elevations in blood pressure. We have explained how the drug mixture caused the increase in blood pressure. We know that the drug mixture has been reported to cause both hemorrhagic and ischemic strokes, both of which result from the elevated blood pressure. We know that alternative causation has been considered and dismissed. It is then logical to consider that Ms. [redacted] experienced a period of vasoconstriction resulting in elevated blood pressure and subsequent dislodgement of plaque or clotting materials which disrupted vascular flow and resulted in infarction of the endothelial tissue in the brain. This is both plausible and scientifically coherent.

7. Experiment

Although human clinical trials are relied upon to establish the efficacy of drugs, and epidemiolgy studies are used in establishing causation relating to adverse drug reactions , animal experimentation is extremely useful in demonstrating concepts used to explain some of the human findings. In addition, studies of the effects of chemicals on cellular processes have also proven useful in being able to understand the mechanisms involved in the toxicological processes being studied.

Experimentation demonstrating various physiological effects of ephedra alkaloids have been reported in both humans and animals. Examples of some of the human studies include a controlled human study showing increased heart rate related to ephedrine,[110] a report of increased blood pressure in healthy medical students dosed with l-norepinepherine,[92] a controlled double blind study of 16 patients showing elevated blood pressure in response to PPA alone and in combination with caffeine,[101] three other studies showing elevated peak blood pressure after PPA use,[88,89,91] a controlled human study showing increased mean supine blood pressure in response to ephedra-alkaloid containing cold medications,[92] and a controlled study showing increased blood pressure, stroke volume and total peripheral resistance in response to treatment with PPA and norephedrine.[107] A study of the effects of pseudoephedrine on 20 hypertensive subjects reported a statistically significant increase in systolic blood pressure and heart rate.[52] The Hemorrhagic Stroke Project also should be considered since it was a well designed epidemiological study showing a clear association between PPA and hemorrhagic stroke.[16]

Animal studies include a study of 47 dogs who had ingested a combination of ma haung (ephedra alkaloids) and guarana (a caffeine source) where dogs were reported to show hyperactivity, seizures, tremors, and behavioral changes with 17% of the dogs dying or euthanized.[93] Another dog study showed that ephedrine and amphetamine augmented the pressor response to norepinephrine.[95] A rat study involving PPA is reported to show dose-dependent increased myocardial necrosis.[99] *Ex-vivo* models also have provided supporting evidence for the contractibility of vasculature muscle. Using a papillary muscle model, ephedrine was reported to produce positive inotropic action on muscle (increased contractibility),[111] and produced contractions when applied to rabbit aortic strips and dog femoral strips.[94]
Animal models have been used to demonstrate the interactions between the ephedra alkaloids and caffeine. Studies in rats have shown a

potentiation of behavioral changes with caffeine and ephedrine.[102,103] Studies in humans also have demonstrated the interactive effects of caffeine on the ephedra alkaloids.[90,101]

While we have only presented limited experimentation above, there is much published literature establishing the agonist action of the ephedra alkaloids and amphetamines on the alpha- and beta-adrenergic receptors and the consequences of these interactions on pressor response and resulting vasculopathy.

8. Analogy

Are there other drugs, chemicals or conditions that simulate the causal relationship which is under scrutiny? Are there other similar situations that parallel the events relating to the causal connection addressed herein?

The chemical structures presented above clearly demonstrate the similarity not only between the eight ephedra alkaloids[112] but also with methamphetamine and amphetamine. There are numerous comparisons between ephedra alkaloids and emphetamines voiced in the published literature including "amphetamine related drug", "amphetamine-like", "chemically similar to amphetamine", and "abused as a substitute for amphetamine.[113] Still other quotes from the literature include "...there are striking similarities between (-) ephedrine and (+) amphetamine as training drugs",[112] [PPA is] "Structurally and functionally similar to amphetamine and ephedrine" and ". . . both of which have been shown to cause central nervous system vasculitis with intracerebral hemorrhage"[114] and, relative to a behavioral study in rats, "These observations indicate that PPA and amphetamine share a similar mechanism of action to the degree that cross-tolerance develops . . .".[115] Even the American Medical Association has stated "Its [PPA] pharmacologic properties are similar to those of ephedrine".[14] Clearly, PPA and the other ephedra alkaloids have an amphetamine-like structure and action.[114,116]

It is clear from the extensive peer-reviewed literature cited above that the ephedra alkaloids including PPA, ephedrine, pseudoephedrine,[77] and other isomers of this series are capable of causing intracerebral hemorrhages and infarctions. It also is clear the sympathomimetic amphetamines picture

above are structurally similar to the ephedra alkaloids and that their physiological action is similar. They both cause increases in blood pressure via the alpha- and beta-adrenergic receptors.[2] Methamphetamine is a scheduled II narcotic. It should not be surprising then that, similar to the ephedra alkaloids, amphetamines are known to cause central nervous system vasculitis and intracerebral hemorrhages[117-122] similar to those caused by the ephedra alkaloids cited above. The analogy requirement of Hill[87] has therefore been accomplished.

CONCLUSIONS AND OPINIONS

I understand that on November 21, 2000, on or about 1537 hours, Ms. [redacted] was found on the floor of the restroom of her workplace in a lethargic condition with her body shaking. She was taken by EMS to Oakwood Hospital where she was diagnosed with an acute cerebrovascular accident. At that time she described a severe headache localized to the right side of her face extending down to her neck with flaccid paralysis of the left arm and leg.

At the time of the accident, Ms. [redacted] was a 44-year-old woman with a 20 pk-yr smoking history having quit in 1991, no alcohol consumption of significance and regular use of caffeine in both tea and coffee. She describes having at least two cups of tea or coffee the morning of her illness. In her deposition and elsewhere, Ms. [redacted] describes having taken six Metab-O-LITE™ pills per day for up to two weeks prior to her stroke. The Metab-O-LITE™ label indicates that each pill contains about 12 milligrams of Ephedra also known as ma huang. In her deposition, Ms.[redacted] could not remember how many Metab-O-LITE™ pills she took on the day of her illness, but typically she would have taken four pills prior to her stroke: two with breakfast and two with lunch. At the time of her admission to the hospital, Ms. [redacted] urine tested positive for amphetamines, which would be consistent with her having taken ephedra alkaloids which are like amphetamines. It is my further understanding that neither she nor her family demonstrated any prior history of either stroke or seizures, but she did have a history of sinus or migraine headaches.

During her hospital stay after her stroke, Ms. [redacted] was examined and found to have had an acute cerebrovascular accident of her right carotid artery with CT scan showing a large area of infarct in the region of the right mid-cerebral artery. The impression of the attending physician was an acute thrombotic cerebrovascular accident, and yet thrombotic factors were found to be negative. Dr. Menawat suggested that the acute

cererbrovascular accident was likely caused by occlusion of the right carotid artery from a plaque rupture. After some diagnostic testing, Dr. Anouti at the Henry Ford Hospital later agreed that "she had experienced some plaque rupture or perhaps carotid dissection."

Subsequent to her hospital stays, Ms. [redacted] began experiencing seizures as noted by Dr. Posadas on February 26, 2001, and Dr. Mangalick on the following day. The latter suggested that the seizures were secondary to the stroke mentioned above and sent a letter to Dr. Posadas on March 26, 2001, describing a second seizure. Subsequent seizures were noted on April 10, 2001, by Dr. Weiss, 2-3 more seizures noted on April 23, 2001, and a total of five seizures noted by Dr. Leuchter after Ms. [redacted]' visit of May 1, 2001. Dr. Leuchter clearly identifies her prior stroke as being a cause of these seizures. Additional seizures are noted by Dr. Leuchter, and he describes Ms. [redacted] condition as "chronic seizure disorder as well as stroke".

At least two neurologists, Drs. Gottesman and Shields have examined Ms. [redacted] medical records and films, and through the differential diagnostic process both have dismissed possible alternative causes of Ms. [redacted] CVA of November 21, 2000, other than ephedra alkaloids from the Metab-O-LITE™ dietary supplement to which she was exposed. Dr. Shields points to the vasoconstrictive properties of the sympathomimetic amphetamine-like alkaloids present in Ephedra and the subsequent flow disruptions and irregular contraction patterns as favoring clot formation. This turbulence also would favor dislodgment of plaque from the endothelial lining of the blood vessel as has been suggested by Drs. Menawat and Anouti. An additional factor which would favor this process beyond direct action by the ephedra alkaloids is the enhanced release of norepinephrine from sympathetic neurons thereby increasing peripheral vasoconstriction and increasing blood pressure even further.

It is clear from the above causation analysis and from the extensive literature on ephedra alkaloids which include PPA and ephedrine that a causal connection exists between exposure to these alkaloids and cerebral vascular accidents including cerebral infarcts and hemorrhages. It is also clear that seizures are frequently observed in Ephedra-medicated patients. In consideration of all the facts in this case, the extensive literature base, the ability to establish beyond doubt a causal connection between ephedra alkaloids and stroke, I opine within a reasonable degree of scientific certainty, that Ms. [redacted]' cerebrovascular accident of November 21, 2000, was caused by her consumption of Metab-O-LITE™ tablets during the two weeks prior to her stroke and the day of her stroke. I reserve the right to supplement this report as additional information becomes available.

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