**Testimony of Sidney M. Wolfe, MD**
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**Before Senate Governmental Affairs Committee, Subcommittee on Oversight of Government Management**
**Hearing on Dangers of Ephedra**
**October 8, 2002**

Senator Durbin and members of the Subcommittee, thank you for the opportunity to testify on this important topic. Your hearing is essential because of the extreme, reckless negligence exhibited by dietary supplement companies who continue to sell ephedra-containing products and because of the industry-enfeebled Department of Health and Human Services, including the FDA, that has thus far allowed the companies to get away with continuing to manufacture and push these deadly drugs.

## The US Military Puts the HHS and the FDA to Shame

From 1997 through part of 2001, there have been 30 deaths among active duty personnel in the armed forces (Army, Air Force, Navy and Marines) in people who were using ephedra alkaloids. All were between the ages of their early 20's and early 40's and had been in good health prior to their deaths. There was no other explanation for their deaths. Since then, there have been three additional deaths associated with the use of ephedra products in the Army alone.[1]

Partly as a result of these 33 deaths and other serious, non-fatal adverse events in the military associated with ephedrine, in July of this year memos were sent to all Army and Air Force military exchanges and commissaries worldwide stating that by the end of August (2002), all ephedra-containing products should be removed from the shelves in these military posts for six months until the results of the HHS ephedra review are released. According to a recent Army/Air Force bulletin, from Fort Monroe, Va. (August 19, 2002)--"Training and Doctrine Command has joined with Forces Command in asking the Army Air Force Exchange Service to remove products containing ephedra, a compound normally found in diet products." It is extremely important that in explaining the basis for issuing this order, Dr. DeKonning, an army physician, stated that "The sale of ephedra-containing products by facilities on TRADOC [training and doctrine command] installations is seen by our soldiers as an affirmation that their use is safe and acceptable."[2]

The U.S. Marine Corps had earlier--in February 2001--banned the sale of ephedra-containing products on its military bases: "The Commandant of the Marine Corps banned the sale of dietary supplements containing ephedra alkaloids, or ephedrine, at Marine Corps Exchange stores worldwide as of February 1.[3]

Sixteen months ago, the Canadian government warned Canadians "not to use products containing the herb Ephedra" because such products "may cause serious, possibly fatal, adverse effects." On January 9 of this year, Health Canada requested a recall of all ephedra products "with labeled or implied claims for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects."

In answering the questions you have provided me, I will add, to the published references in our petition, information obtained since it was filed.

**What is the basis for our September, 5, 2001 HHS petition (filed with Dr. Ray Woosley, now of the University of Arizona) to ban the manufacture and sale of all ephedra-containing dietary supplements?**

The answer to this question must start out with two other questions:

Do drugs which are related to epinephrine (adrenaline) such as ephedrine, phenylpropanolamine, amphetamines and similar drugs cause an increase in blood pressure, constriction of blood vessels, an increase in heart rate or an increase in cardiac arrhythmias? The answer is unequivocally yes, and this has been known for decades.

Is there evidence that these drugs can cause strokes and heart attacks in people because of causing an increase in blood pressure, constriction of blood vessels, heart rate or cardiac arrhythmias?

In addition to the section in our petition presenting evidence for cardiovascular toxicity of ephedra (see appendix), we have obtained a copy of an internal March 28, 2000 FDA memo from Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) in response to being asked to review the strength of the evidence linking ephedra with life-threatening cardiovascular events and strokes. After a review by CDER's Office of Postmarketing Drug Risk Assessment (OPDRA), Dr. Woodcock concluded that "...at least 108 of the reports [clinically significant cardiovascular and central nervous system adverse event reports] OPDRA analyzed provide very strong evidence in support of a causal relationship between EADS [ephedra alkaloid-containing dietary supplements] and the adverse events, particularly in light of the known pharmacodynamic effects of ephedrine alkaloids."[4]

**What is the incongruity in FDA banning PPA (phenylpropanolamine) but allowing ephedra to stay on the market?**

Given that there are now more reported cases of death, heart attacks, stroke and other adverse effects associated with ephedra than with PPA at the

time of its ban, the situation represents a dangerous déjà vu. We are now, with ephedra, where we were 10 years ago with PPA: clear, unequivocal evidence of danger but a time-delaying "need" by the industry to conduct studies. (FDA unfortunately bought into the need for a case control study on PPA 10 years ago). With PPA, dozens or more lives were lost and many people permanently disabled between the time the FDA clearly should have acted and when they finally got the drug (PPA) off the market. To repeat this fatal mistake with ephedra is to fail to learn the lessons of history.

**Since we have petitioned the FDA to ban other weight loss products such as Meridia (sibutramine, Abbott), what benefit/risk analysis should be applied to weight loss products?**

Over 30 years ago, in June 1968, FDA Medical Officer Dr. Robert O. Knox refused to approve the New Drug Application (NDA) for a diet drug. This disapproval touched off a dispute between the FDA and the drug's manufacturer, A.H. Robbins, that eventually led to the drug's approval and Dr. Knox's transfer to another area within the Agency. His reason: obesity is a chronic disease and there is no evidence that these drugs affect the course of the disease over the long term.

The drug Dr. Knox refused to approve was fenfluramine (Pondimin), a drug that ultimately became the "fen" portion of the notorious "fen/phen" combination, the portion that was removed from the market on September 15, 1997 because it caused heart valve damage and a potentially fatal adverse reaction of the lungs known as primary pulmonary hypertension.

At the time of our petition to ban Meridia on March 19th of this year, there were 19 reported cardiovascular deaths in people using the drug, again, far fewer than the number with ephedra. The fact that there is no evidence of long-term benefit with either drug and there is evidence of shorter-term risk means that the benefit/risk ratio for both is extremely unfavorable to patients.

**Discuss what is known about the dosages taken by those experiencing serious adverse effects from ephedrine/ephedra. Is there a safe dose?**

In a recent published review of FDA adverse reaction reports by researchers from New England Medical Center in Boston, in 36 of 37 patients with heart attacks, strokes or sudden deaths, the use of ephedra (ma huang) was reported to be within the manufacturers' dosing guidelines.[5] There are also a number of reports in which a so-called pharmacologic autopsy--post-mortem measurement of urine, blood and tissue levels--found low levels of ephedra consistent with recommended use. Given that there is no standardization of the amount appearing in the product and, more importantly, that there is enormous variation from person to person in sensitivity to such drugs, no dose is the only safe dose.

**Discuss the effects that additional compounds such as caffeine have on the safety profile of ephedra, given that it is usually sold in combination with such stimulants.**

Both caffeine and ephedra can stimulate the sympathetic nervous system so their combined use increases the cardiovascular risks. In addition, the frequent use of these products in the context of exercise, also a stimulant to the sympathetic nervous system, makes for a triple dose of stimulation--in combination with ephedra and caffeine--which probably accounts for the growing number of deaths while young, otherwise healthy people are exercising.

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In July 1995, according to the agency, "FDA proposed banning OTC bronchodilators containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride because of abuse and misuse. According to the U.S. Drug Enforcement Administration, ephedrine is being used to make illegal drugs. And, the FDA has found that some drug manufacturers promote ephedrine for unapproved uses, such as weight control and muscle enhancing." The fact that the FDA has not finalized this proposed ban of ephedrine in OTC products should not be used as an excuse for the failure to ban dietary supplements containing ephedra. The proposed OTC ban is still in the works.

This is not and has never been a question of scientific or medical evidence. It is a question of politics, and the extraordinarily dangerous political cowardice of the FDA and HHS Secretary Thompson in the face of massive lobbying by ephedra-makers in Washington. Is the FDA still part of the Public Health Service or is it a drug sales promoting adjunct to the pharmaceutical and dietary supplements industries? De facto drug pushers include those who refuse to use their legal authority to remove a well-documented hazard to the public health from the market. There is no doubt that these products will be banned in the United States. The question is not whether, but when. Delaying tactics such as the Rand review are costing lives as the day of reckoning for ephedra is thereby delayed. There are few issues that the AMA and Public Citizen agree on. Tobacco and ephedra are two of these. The FDA has been rejecting the opinions of its own consultants and staff (such as Dr. Woodcock) on the dangers of ephedra alkaloids.

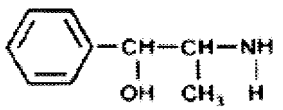
## Appendix

The FDA funded the review by Benowitz, which found hypertension to be the most common manifestation of ephedrine alkaloid dietary supplement toxicity.[6] Zahn reports a 21-year-old man presenting to the emergency department with a blood pressure of 220/110 after ingesting *herbal ecstasy*, a common name for an ephedrine alkaloid dietary supplement.[7]

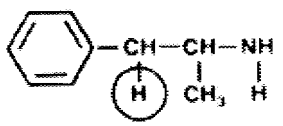
Sixty-nine cases of ephedrine alkaloid dietary supplement associated stroke are represented in the SN/AEMS data set. Ephedrine alkaloid dietary supplements account for 81% of all dietary supplement related strokes. Alarmingly, stroke has been reported with the use of an ephedrine alkaloid dietary supplement in an individual of exceptional health without any other known risk factors for a cerebrovascular accident.[8] Bruno et al. report three separate incidences of stroke associated with the use of street drugs containing ephedrine exclusively[9] and the Hemorrhagic Stroke Project documented the increased susceptibility to stroke found in women using phenylpropalamine (PPA), a metabolic breakdown product of ephedrine and another member of the ephedrine alkaloid family.[10] A vasculitis-like beading pattern of the cerebral arteries is a common factor to many of the ephedrine alkaloid stroke reports. [11,12,13]

The following chart shows the close chemical structures of PPA, ephedrine and amphetamine. Notice that PPA is identical to ephedrine except for the absence of a methyl (CH3) group. In fact, the body metabolizes a small portion of ephedrine to PPA which is also called norephedrine (nor meaning no methyl group).

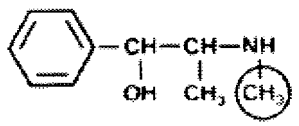
PHENYLPROPANOLAMINE




AMPHETAMINE




EPHEDRINE



Ephedrine dietary supplements have been implicated in 62 instances of arrhythmia in the SN/AEMS data set. Zahn reports ventricular arrhythmia temporally associated with a patient's use of an ephedrine alkaloid dietary supplement.[14] The patient stabilized after emergent treatment with lidocaine. Such ventricular arrhythmia may easily degenerate into ventricular fibrillation and cardiac arrest as described by Haller and Benowitz.[15] In the over the counter medication market, ephedrine alkaloid based cold medications have been shown to induce arrythmias. Pseudoephedrine, at recommended doses, was implicated in causing an arrhythmia in a healthy man with no known risk factors.[16] Onuigbo's case report of arrhythmia in a pregnant woman shows that unwittingly combining sympathomimetics places patients at perilous risk.[17] The fact that all of the cases of arrhythmia resolve and fail to recur in the absence of the offending agent is compelling evidence in favor of ephedrine alkaloid's causal role.

Coronary vasospasm due to the ingestion of sympathomimetics has been shown to result in chest pain and myocardial infarction / heart attack. Ephedrine alkaloid dietary supplements contributed to 88 reports of chest pain and 32 cases of myocardial infarct / heart attack in the SN/AEMS data set. Traub reports a 19-year-old male bodybuilder who suffered an inferolateral myocardial infarction after using the recommended dosage of an ephedrine alkaloid dietary supplement.[18] This patient had no known risk factors for heart disease and no significant findings on cardiac catheterization. In a controlled cross-sectional study of chest pain admissions at a pediatrics emergency department, James found that ephedrine exposure was associated with chest pain in adolescents.[19] Wiener describes a 28-year-old man with no known cardiac risk factors who suffered a myocardial infarct after taking the recommended dose of a pseudoephedrine decongestant.[20] This apparently inherent ability of ephedrine alkaloids to provoke chest pain and induce myocardial infarction in healthy patients is of particular concern because of the implications for vulnerable patients using other medications or with previously undiagnosed underlying medical conditions. Note that some of these adverse cardiovascular events can occur at the recommended dose.

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[1] Telephone conversation with Mike Heath, Pharm.D. Senior Pharmacist, U.S. Army, Consultant for the US Army Surgeon General, Washington DC.

[2] Announcement of recent Army/Air Force worldwide ban of sale of ephedra-containing products in military exchanges. A similar memo was sent concerning the ban of sales in commissaries (these are different from exchanges. http://www.army.mil/usar/news/2002/08august/ephedra.html (Accessed October 7, 2002)

[3] Announcement from Marine Corps Air Station Miramar, February 9, 2001 Order issued by General James L. Jones.

[4] Memo from Dr. Janet Woodcock, March 28, 2000, to FDA CFSAN (Center for Food Safety and Nutrition) Director Joe Levitt.

[5] Samenuk D, et al. Adverse cardiovascular events temporally associated with Ma Huang, an herbal source of ephedra. Mayo Clin Proc, 2002;77:12-16.

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[14] Zahn, op. cit.

[15] Haller, op. cit.

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