*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

September 5, 2001

Tommy Thompson, Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

Dear Secretary Thompson,

The Public Citizen Health Research Group, representing 135,000 members, petitions the Food and Drug Administration (FDA) to ban the production and sale of dietary supplements containing ephedrine alkaloids*. These dietary supplements include, but are not limited to, those containing ephedra, ephedra extract, and ma-huang. The grounds for FDA action are that these products present "a significant or unreasonable risk of illness or injury under conditions of use suggested or recommended in the labeling" or, if the label is not specific, "under ordinary conditions of use." Therefore, under 21 USC 331(a) and 342 (f) HHS must declare these products adulterated and issue an immediate ban on their sale and production.[1]

You are known to be extremely concerned about food safety and these dangerous "food supplements" pose a clear threat to the safety of the food supply in this country for those who use them. Among the frequent targets of these ephedrine-containing products are young people for whom they are being promoted as athletic performance enhancing. Due to the gravity of the situation, the Canadian equivalent of the Department of Health and Human Services, Health Canada, recently issued a public advisory in June 2001 "warning consumers not to use products containing the herb Ephedra".[2] Health Canada based its decision to release the advisory, in part, on the United States' FDA adverse event reports. We urge you to immediately issue a similar advisory warning Americans not to use ephedra-containing dietary supplement products while you review our petition for the ban requested above.

We have obtained an internal FDA analysis of recent adverse event reports to FDA's own database that demonstrates that the ephedrine alkaloids are the most lethal and otherwise dangerous dietary supplements. We also

* The ephedrine alkaloids include: ephedrine, pseudoephedrine, methylephedrine, norephedrine, and norpseudoephedrine. Norephedrine, is also known as phenylpropanolamine, recently banned by the FDA. These compounds are able to elicit physiological responses similar to sympathetic nervous system catecholamines and are hence known as sympathomimetics. These compounds are known to increase the risk for hypertension, stroke and heart attacks and agents that block their effects, such as beta blockers, decrease the risk of these life-threatening adverse events.

Ralph Nader, Founder
1600 20th Street NW • Washington, DC 20009-1001 • (202) 588-1000 • www.citizen.org

Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

obtained an FDA analysis of data collected by the American Association of Poison Control Centers (AAPCC) which shows that there was a sharp increase from 1997 through 1999 in the number of adverse event reports for these highly pharmacologically active and dangerous drugs masquerading as "dietary supplements".

A. ACTIONS REQUESTED

1. A ban on the sale and production of ephedrine alkaloid dietary supplements.
2. An immediate FDA advisory to stop the use of ephedrine alkaloid dietary supplements due to the established risks of injury.

B. STATEMENT OF GROUNDS

FDA Analysis of FDA Adverse Event Reports

The recently updated review of FDA's Center for Food Safety and Applied Nutrition's (CFSAN) Special Nutritionals Adverse Event Monitoring System (SN/AEMS), including data collected from January 1993 until February 2001, shows that ephedrine alkaloid dietary supplements are associated with more reports of deaths, myocardial infarctions, cardiac arrhythmias, hypertension, stroke and seizure events than all other dietary supplements combined. According to the FDA analysis (see attachment 1), during this interval there were:

- 3308 adverse events for all dietary supplements, 1398 of these (42%) for the ephedrine alkaloids (EA)
- 137 reports of death, 81 deaths (59%) associated with EA
- 38 reports of myocardial infarction/heart attack, 32 reports (84%) associated with EA
- 98 reports of cardiac arrhythmias, 62 (63%) associated with EA
- 144 reports of hypertension, 91 (63%) associated with EA
- 85 reports of stroke, 69 (81%) associated with EA
- 121 reports of seizure, 70 (58%) associated with EA

Two earlier FDA-commissioned reviews of a much smaller number of adverse events reported to the FDA involving the use of ephedrine alkaloids (did not include data from 2000 and 2001) confirmed the cardiac toxicity of these chemicals. The first study found that 47% of cases involved the cardiovascular system (17 cases of hypertension, 13 with palpitations or fast heartbeat, 10 strokes). There were also 7 reports of seizures.[3] The second study, by Dr. Woosley (a co-petitioner for this ban) found that of the 104 reports in which causation by ephedrine alkaloids was very likely, there were 10 cases of sudden death, 9 cardiac arrhythmias, another 23 possible arrhythmic events, 3 heart attacks, 10 cases of chest pain and 15 severe strokes.[4]

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

FDA Analysis of AAPCC Data

The second source of data about ephedrine alkaloids is a recent FDA analysis of data collected by the American Association of Poison Control Centers (AAPCC), which clearly shows that the number of serious adverse events associated with ephedrine alkaloid dietary supplements is on the rise (table 1)(see also attachment 2). The total number of adverse events related to EA increased from 211 in 1997 to 407 in 1999, an increase of 196 reports per year, almost a doubling from the number of reports in 1997.

Year	All Adverse Events Related To Ephedrine Alkaloid Dietary Supplements	Cardiovascular Adverse Events Related To Ephedrine Alkaloid Dietary Supplements	CNS Adverse Events Related To Ephedrine Alkaloid Dietary Supplements	Gastrointestinal Adverse Events Related To Ephedrine Alkaloid Dietary Supplements
1997	211	85	11	70
1998	258	127	142	74
1999	407	204	211	140

Table 1 – Shows the adverse events related to ephedrine alkaloid dietary supplements in the years 1997-1999. The adverse events are divided into cardiovascular, central nervous system (CNS), and gastrointestinal subsets. Source: AAPCC.

Between 1997 and 1999, AAPCC reports of central nervous system adverse events with ephedrine alkaloid dietary supplements increased nineteen fold from 11 to 211. Cardiovascular adverse events increased 2.4 fold from 85 to 204, while gastrointestinal adverse events doubled from 70 to 140.

Underreporting Flaws Result in Fewer Adverse Events

The AAPCC represents a collection of reports made by consumers from their homes (77%) or from health care facilities (13%).[5] Since the AAPCC relies on a voluntary reporting system, these numbers likely underestimate the number of adverse events occurring in the population. The SN/AEMS data is collected from FDA's MedWatch program, FDA's field offices, other federal, state, and local public health agencies, letters and phone calls from consumers and health professionals. Due to the voluntary nature of the SN/AEMS reporting system, these figures sorely understate the scope and magnitude of the problems caused by ephedrine alkaloid dietary supplements, as was determined by the Office of the Inspector General of the Department of Health and Human Services.[6]

The seriousness of the underreporting to the FDA database is demonstrated by the fact that there were a total of 1398 adverse event reports

with ephedrine alkaloid dietary supplements in the FDA database during an eight year period (1993-early 2001), but there were 876 ephedrine alkaloid dietary supplement adverse event reports to the AAPPC data base in just three years. Furthermore, the Texas Department of Health reported approximately 500 adverse events in the period between December 1993 and September 1995.[7] The fact that in under two years a single state could collect over a third as many ephedra adverse event reports as SN/AEMS has gathered between 1993 and February, 2001 speaks to the pitiful inadequacy of the current FDA system. Furthermore, dietary supplement labeling does not include instructions on how to contact either the FDA or the AAPCC which increases the likelihood of underreporting of adverse events. When both of these limited monitoring systems indicate that a product is causing hundreds of adverse events, thousands of consumers are likely being affected.

Pharmacological Properties of Ephedrine Alkaloid Dietary Supplements

The ephedrine alkaloid dietary supplements are as dangerous as prescription or over the counter ephedrine alkaloid drugs because ephedrine alkaloid dietary supplements contain the same compounds found in synthetically synthesized ephedrine alkaloid medications and, hence, have the same pharmacological and toxicological activity.[8,9] In fact, a recent study by Lee finds that ephedra extract had a higher neuro-cytotoxic potential than a standardized dose of synthetic ephedrine hydrochloride alone.[10] Lee suggests that this increased toxic effect can be attributed to the combination of different ephedrine alkaloids or the presence of other unknown compounds in ephedra extract but not present in pure synthetic ephedrine. Furthermore, Glennon describes an experiment in which he demonstrates an ephedrine alkaloid dietary supplement's ability to mimic the effects of amphetamines.[11] Whereas the dose of ephedrine alkaloids found in prescription or over the counter medications is constant and known, such consistency is not found with ephedrine alkaloid dietary supplements. Gurley's study of 20 different ephedrine alkaloid dietary supplements exposed the contents of these products. It was determined that ephedrine alkaloid dietary supplements contain combinations of different ephedrine alkaloids including norpseudoephedrine, a Schedule IV controlled substance. While combining ephedrine alkaloids with stimulants to produce an amphetamine-like effect is prohibited by the FDA, Gurley found combinations of ephedrine alkaloids and caffeine containing substances to be commonplace in the dietary supplements he studied.[12] Therefore, it is clear that ephedrine alkaloid dietary supplements are at least as dangerous as ephedrine alkaloid medications. Thus, it is essential that the adverse event data for ephedrine alkaloid drugs be considered along with the growing body of evidence that ephedrine alkaloid dietary supplements are unsafe. We briefly review the variety of adverse events reported in the literature as a means of further demonstrating that ephedrine alkaloid dietary supplements present an unreasonable risk of illness and injury to American consumers.

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Cardiovascular Complications of Ephedrine Alkaloids Use

Randy Sasich, M.D., the son of our colleague Larry Sasich, Pharm D., MPH, was in an internal medicine residency at Barnes-Jewish, the main teaching hospital of Washington University in St. Louis. Within just a 7-month period, he took care of two patients admitted to the coronary care unit because an ephedrine alkaloid dietary supplement (Metabolife) had induced life-threatening cardiac arrhythmias. He is aware of a third patient, also discussed below, who used Metabolife and experienced an arrhythmia but was not hospitalized:

Case 1 –April 1999. This patient, a female in her late fifties, presented at the emergency room with a dangerously rapid rate of contractions of one of the large chambers of the heart, or ventricles (ventricular tachycardia or V-tach), after using an ephedrine alkaloid dietary supplement for weight control. She was admitted to the coronary care unit for observation. She was subsequently discharged.

Case 2 –April 1999. This patient, a female in her late thirties, suffered a heart attack (acute anterior myocardial infarct) and cardiac arrest while using an ephedrine alkaloid dietary supplement for weight control. She was a smoker but had no evidence of previous atherosclerotic disease of any significance. She suffered brain damage due to a lack of circulation.

Case 3 –October 1999. A female nurse, age unknown, experienced a rapid heart rate while using an ephedrine alkaloid dietary supplement. The rapid rate was documented by her colleagues using an electrocardiogram (ECG or EKG). She was observed until her rapid rate resolved.

These three cases of cardiac injury from ephedrine alkaloid dietary supplements in one hospital in only seven months is a further indication that ephedrine alkaloid toxicity is a much more common problem than the FDA and AAPCC data indicate.

The AAPCC data shows 416 ephedrine alkaloid dietary supplement related cardiovascular adverse events reported between 1997 and 1999. According to the SN/AEMS data, the most common manifestations of injury were hypertension, stroke, arrhythmia, chest pain, and palpitations (figure 1, table 2).

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

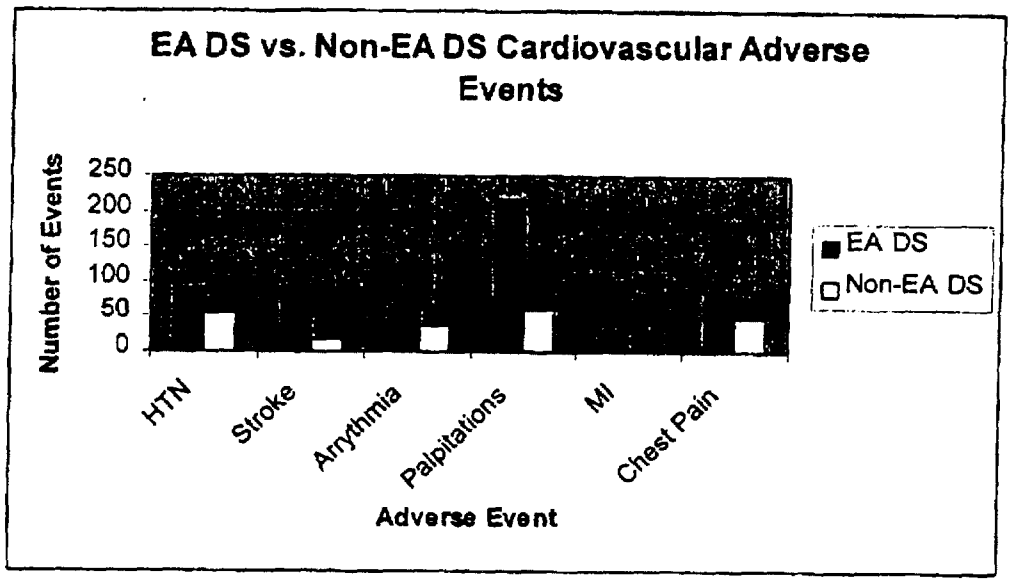


Figure 1 – Comparison of the cardiovascular adverse events of ephedrine alkaloid dietary supplements (EADS) with those of non-ephedrine alkaloid dietary supplements. Hypertension (HTN), Palpitations (includes: palpitations, pounding, racing, and rapid heart), MI (Myocardial Infarction/Heart Attack). Source: SN/AEMS, FDA.

Adverse Event	Number of Adverse Events Associated with EA DS	Number of Adverse Events Associated with Non-EA DS	Percentage of DS Adverse Events Associated with EA DS
Hypertension	91	53	63%
Stroke	69	16	81%
Arrhythmia	62	36	63%
Palpitations	218	60	78%
Myocardial Infarction/ Heart Attack	32	6	84%
Chest Pain	88	47	65%

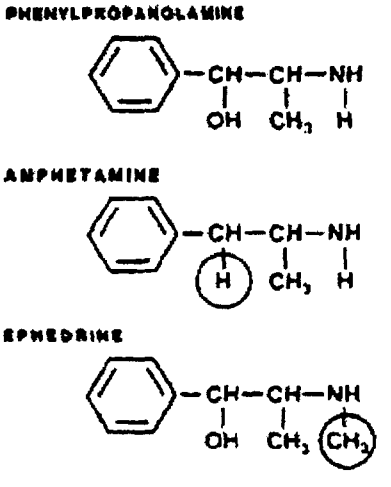
Table 2 – The distribution of cardiovascular adverse events related to dietary supplements (DS) arranged by presence of ephedrine alkaloids (EA). Note that palpitations also include: pounding, racing, and rapid heart. Source: SN/AEMS, FDA.

The FDA funded the review by Benowitz, which found hypertension to be the most common manifestation of ephedrine alkaloid dietary supplement toxicity.[13] 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.[14]

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.[15] Bruno et al. report three separate incidences of stroke associated with the use of street drugs containing ephedrine exclusively[16] 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.[17] A vasculitis-like beading pattern of the cerebral arteries is a common factor to many of the ephedrine alkaloid stroke reports.[18,19,20]

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).



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.[21] 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.[22] 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.[23] Onuigbo's case report of arrhythmia in a pregnant woman shows that unwittingly

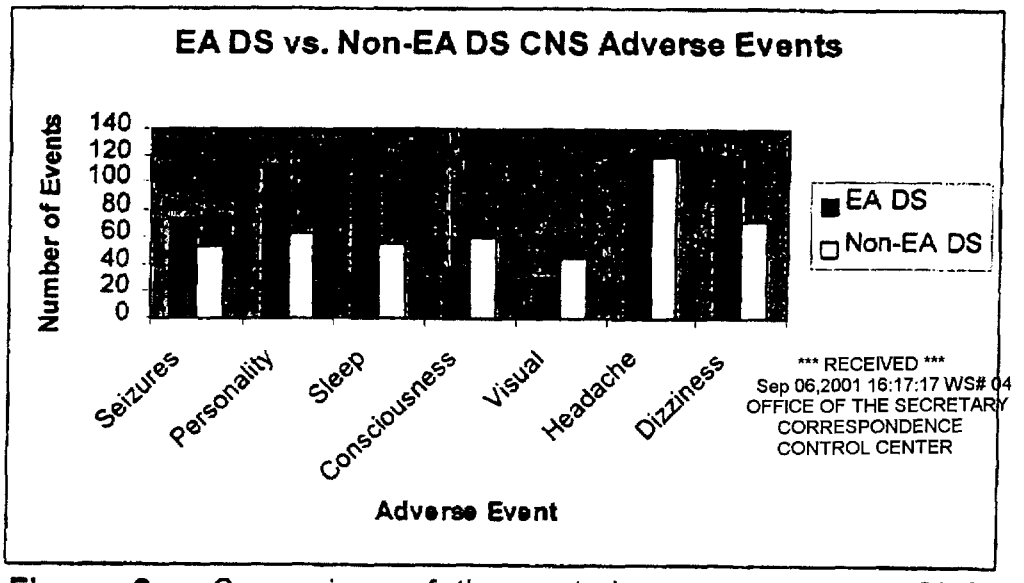
combining sympathomimetics places patients at perilous risk.[24] The fact that all of the cases of arrhythmia resolve and fail to recur in the absence of the offending agent is compelling evidence in favor of ephedrine alkaloid's causal role.

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.[25] 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.[26] 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.[27] 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.

Intuitively, we would expect that polypharmacy or medical conditions would increase the risk of injury due to ephedrine alkaloids. Pederson describes a case of concomitant use of bupropion and pseudoephedrine leading to myocardial ischemia in a 21-year-old man.[28] Also, Derreza documents an acute myocardial infarct in a heavy smoker after using a pseudoephedrine decongestant.[29] The illicit use of ephedrine as a cheap alternative to amphetamines has been shown to induce myocardial infarction in an individual with a history of substance abuse.[30]

Central Nervous System Complications of Ephedrine Alkaloid Use

The AAPCC data reports at least 364 neurologic adverse events associated with the use of ephedrine alkaloids in the period between 1997 and 1999. Compared to *all* other dietary supplements combined, ephedrine alkaloid dietary supplements were responsible for the majority of reports of seizures, personality disorders, sleep disturbances, and headaches in the FDA database (SN/AEMS). The literature also describes cases of agitation, hallucination, seizures, psychoses, and mania.[31, 32, 33, 34, 35] As with the arrhythmia reports described above, all psychiatric manifestations resolved after the offending agent was removed.



*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Figure 2 – Comparison of the central nervous system (CNS) adverse events of ephedrine alkaloid dietary supplements with those of non-ephedrine alkaloid dietary supplements. Personality (includes: mania, personality change, depression, mood changes, agitation, violence, rage, anger, and panic attack), Sleep (includes: insomnia, and altered sleep), Consciousness (includes: incoherence, confusion, disorientation, delirium, and coma), Visual (visual disturbance). Source: SN/AEMS, FDA.

In a 1970 study of the physiologic and behavioral effects of ephedrine, Martin found that ephedrine was able to produce subjective effects similar to amphetamines and proposed that they had comparable abuse potential.[36] A more recent study by Chait finds the use of a single alkaloid, ephedrine, has a less addictive profile than amphetamines.[37] However, another study shows that the effects of ephedrine are potentiated by the concomitant use of caffeine. In fact, the combination of ephedrine and caffeine at individually sub-threshold quantities are synergistically able to produce an effect that is similar to that of amphetamines.[38] This is especially significant because many ephedrine alkaloid dietary supplements also contain caffeine or other stimulants. The SN/AEMS data includes six reports of addiction, withdrawal and dependence. A study of 64 female weightlifters revealed a 56% ephedrine use rate. Almost all had tried to cut down their use or tried to stop out of concern for side effects.

Some women reported continued use of ephedra-containing products despite adverse effects due to withdrawal symptoms such as fatigue and weight gain. Furthermore, 7 out of 36 users described frank ephedrine dependence.[39] The sale of ephedrine alkaloid dietary supplements for the indications of weight loss and energy boosting almost guarantees a pattern of abuse. Since many consumers of dietary supplements consider them to be natural, and hence safe, a certain element of informed consent is lost when users are not properly educated about the likelihood of developing chemical dependence. This

possibility is of particular concern in light of the increased risk of cardiovascular and central nervous system injury described above.

Genito-urinary Complications of Ephedrine Alkaloid Use

Powell and Blau independently report cases of ephedrine nephrolithiasis (kidney stones) in two patients consuming ephedrine alkaloid products.[40, 41] Powell's analysis of his patient's stone and that of seven others identified the substrate of the calculi as combinations of ephedrine, norephedrine and pseudoephedrine. The fact that there is only one kidney stone reported to the FDA database further underscores the fact that underreporting is a major weakness of the FDA database.

Gastrointestinal Complications of Ephedrine Alkaloid Use

The AAPCC data contains 284 reports of adverse gastrointestinal events. Twelve cases of ephedrine alkaloid dietary supplement related hepatitis have been reported to SN/AEMS. In the literature, two separate case reports of acute necro-inflammatory hepatitis demonstrate a temporal association with ephedrine alkaloid dietary supplements. In Nadir's report, the patient briefly discontinued the use of the ephedrine alkaloid dietary supplement after noticing jaundice. Upon re-exposure to a single dose of the product the patient's symptoms acutely worsened. Permanent removal of the ephedrine alkaloid agent resulted in gradual clinical and biochemical improvement without any future recurrence.[42] Borum speculates that ephedrine alkaloid dietary supplements may play a role in exacerbating a sub-clinical autoimmune condition.[43]

Several reports of transient ischemic colitis associated with the use of decongestants containing pseudoephedrine have been documented.[44, 45] Dowd's report asserts that varying estrogen levels related to birth control use or perimenopausal status may contribute to pseudoephedrine's vasoconstrictive role in ischemic colitis. Lichtenstein's report of a 32-year-old man with ischemic colitis secondary to pseudoephedrine use leads him to believe that pseudoephedrine may be an independent risk factor for ischemic colitis. In all the cases mentioned, the clinical symptoms and histopathological signs resolved after discontinuation of pseudoephedrine.

Dermatological Complications of Ephedrine Alkaloid Use

The SN/AEMS data include 50 reports of hypersensitivity reactions to ephedrine alkaloid dietary supplements. Whereas no reports of allergic reactions to ephedrine alkaloid dietary supplements exists in the literature, pseudoephedrine has been found to cause a large number of skin eruptions.[46, 47, 48, 49, 50, 51, 52, 53, 54] Cavannah and Ballas recount the condition of an 18-year-old female evaluated for immunodeficiency causing recurrent toxic shock syndrome. History revealed that each of the episodes was preceded by upper respiratory

infections that she self-medicated with over the counter pseudoephedrine. When advised to avoid pseudoephedrine products the patient remained symptom free.

The immunopathogenic potential of pseudoephedrine may help to explain the cerebrovascular reactions and inflammatory hepatitis seen in ephedrine alkaloid dietary supplement users. In fact, patch testing of ephedrine by Sanchez was able to precipitate the same exanthema produced by pseudoephedrine demonstrating that ephedrine is able to interact with the immune system in a fashion similar to pseudoephedrine.[55] Thus, the potential for ephedrine to initiate or exacerbate an autoimmune condition is a real possibility. All the case reports of sensitivity indicated there was resolution of symptoms once the agent is removed. This intervention (drug discontinuation) requires that either the treating physician or the patient make the association between the clinical picture and the consumption of an ephedrine-containing product.

C. ENVIRONMENTAL IMPACT

Nothing requested in this petition will have an impact on the environment.

D. ECONOMIC IMPACT

The only potential loss of income is to the manufacturers and distributors of ephedrine alkaloid dietary supplements. Potentially there will be savings on the productivity of citizens who otherwise would have been injured by ephedrine alkaloid dietary supplements. Also, the health care savings for avoiding the need to treat cardiovascular, central nervous system, and other injuries due to these products.

E. CERTIFICATION

We certify that, to our best knowledge and belief, this petition includes all information and views which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Conclusions

The wide range of adverse events associated with the consumption of ephedrine alkaloids demonstrates a significant and unreasonable risk of illness and injury. Especially because these risks are not balanced by any long-term benefits, it is imperative that you act quickly and decisively to prevent future death and injury. This problem is exacerbated by the underreporting of ephedrine alkaloid dietary supplement use to physicians by patients, and by health care professionals to national data collection authorities. The April 2001 report of the Department of Health and Human Services Inspector General revealed that voluntary data collection methods currently available to the FDA are woefully

inadequate, and fail to account for 99% of all adverse events associated with dietary supplements. The problem of underreporting is multifaceted and is beyond the scope of this petition. Even with the limited data available via the SN/AEMS, AAPCC, and the medical literature it is clear that ephedrine alkaloid dietary supplements present an unreasonable risk of illness *and* injury to American consumers. It is your responsibility to act upon our recommendation to remove ephedrine alkaloid dietary supplements from the market. Failure to do so will surely result in increased death and injury due to an unsafe product that has no proven benefit to consumers.

We expect a rapid response to this urgent petition. From the perspective of defending the public health, you must be willing to take on this drug (ephedra)-pushing part of the dietary supplement industry.

Sincerely,

Sidney M. Wolfe, MD, Director,
Public Citizen's Health Research Group

Amer Ardati, Research Associate,
Public Citizen's Health Research Group

Ray Woosley, MD, Ph.D.
Vice-President for Health Sciences,
University of Arizona Medical Center

(Dr. Woosley's opinions do not necessarily represent the views of the University of Arizona)

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

---

[1] 21 USC 331(a), 342 (f)

[2] Advisory not to use products containing Ephedra or ephedrine. Health Canada **2001**, June 14. http://www.hc-sc.gc.ca/english/archives/warnings/2001/2001_67e.htm

[3] Haller, C. A.; Benowitz, N. L. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* **2000**, *343*, 1833-8

[4] Woosley, R. Letter to the FDA. **1999**, August 18

[5] Litovitz, T. L.; Klein-Schwartz, W.; White, S.; Cobaugh, D. J.; Youniss, J.; Drab, A.; Benson, B. E. 1999 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* **2000**, *18*, 517-74

[6] Office of the Inspector General. Adverse event reporting for dietary supplements, an inadequate safety valve. Washington: Department of Health and Human Services, **2001**, April, OEI-01-00-00180

[7] From the Centers for Disease Control and Prevention. Adverse events associated with ephedrine-containing products--Texas, December 1993-September 1995. *JAMA* **1996**, *276*, 1711-2

[8] Gurley, B. J.; Gardner, S. F.; Hubbard, M. A. Content versus label claims in ephedra-containing dietary supplements. *Am J Health Syst Pharm* **2000**, *57*, 963-9

[9] Hardman, J.G.; Limbird, L.E. Goodman and Gilman's Pharmacological Basis of Therapeutics. 9th ed. New York : McGraw-Hill, Health Professions Division, c**1996**, 221-4

[10] Lee, M. K.; Cheng, B. W.; Che, C. T.; Hsieh, D. P. Cytotoxicity assessment of Ma-huang (Ephedra) under different conditions of preparation. *Toxicol Sci* **2000**, *56*, 424-30

[11] Glennon, R. A.; Young, R. (+)Amphetamine-stimulus generalization to an herbal ephedrine product. *Pharmacol Biochem Behav* **2000**, *65*, 655-8

[12] Gurley, op. cit.

[13] Haller, op. cit.

[14] Zahn, K.; Li, R.; Purssell, R. Cardiovascular toxicity after ingestion of "herbal ecstacy". *Journal of Emergency Medicine* **1999**, *17*, 289-91

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

[15] Vahedi, K.; Domigo, V.; Amarenco, P.; Bousser, M. Ischaemic stroke in a sportsman who consumed MaHuang extract and creatine monohydrate for body building. *Journal of Neurology, Neurosurgery & Psychiatry* **2000**, *68*, 112-3

[16] Bruno, A.; Nolte, K.; Chapin, J. Stroke associated with ephedrine use. *Neurology* **1993**, *43*, 1313-6

[17]Kernan, W. N.; Viscoli, C. M.; Brass, L. M.; Broderick, J. P.; Brott, T.; Feldmann, E.; Morgenstern, L. B.; Wilterdink, J. L.; Horwitz, R. I. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* **2000**, *343*, 1826-32

[18] Stoessl, A.; Young, G.; Feasby, T. Intracerebral haemorrhage and angiographic beading following ingestion of catecholaminergics. *Stroke* **1985**, *16*, 734-6

[19] Yin, P. Ephedrine-induced intracerebral hemorrhage and central nervous system vasculitis. *Stroke* **1990**, *21*, 1641

[20] Wooten, M. R.; Khangure, M. S.; Murphy, M. J. Intracerebral hemorrhage and vasculitis related to ephedrine abuse. *Ann Neurol* **1983**, *13*, 337-40

[21] Zahn, op. cit.

[22] Haller, op. cit.

[23] Billings, C.; Ralston, R.; Hare, D. Untoward effects of a sympathomimetic amine. *Aerospace Medicine* **1974**, *45*, 551-2

[24]Onuigbo, M.; Alikhan, M. Over-the-counter sympathomimetics: a risk factor for cardiac arrhythmias in pregnancy. *Southern Medical Journal* **1998**, *91*, 1153-5

[25] Traub, S.; Hoyek, W.; Hoffman, R. Dietary supplements containing ephedra alkaloids. *New England Journal of Medicine* **2001**, *344*, 1096; discussion 109-7

[26]James, L.; Farrar, H.; Komoroski, E.; Wood, W.; Graham, C.; Bornemeier, R.; Valentine, J. Sympathomimetic drug use in adolescents presenting to a pediatric emergency department with chest pain. *Journal of Toxicology - Clinical Toxicology* **1998**, *36*, 321-8

[27]Wiener, I.; Tilkian, A.; Palazzolo, M. Coronary artery spasm and myocardial infarction in a patient with normal coronary arteries: temporal relationship to pseudoephedrine ingestion. *Catheterization & Cardiovascular Diagnosis* **1990**, *20*, 51-3

[28] Pederson, K.; Kuntz, D.; Garbe, G. Acute myocardial ischemia associated with ingestion of bupropion and pseudoephedrine in a 21-year-old man. *Canadian Journal of Cardiology* **2001**, *17*, 599-601

[29] Derreza, H.; Fine, M.; Sadaniantz, A. Acute myocardial infarction after use of pseudoephedrine for sinus congestion. *Journal of the American Board of Family Practice* **1997**, *10*, 436-8

[30]Cockings, J.; Brown, M. Ephedrine abuse causing acute myocardial infarction. *Medical Journal of Australia* **1997**, *167*, 199-200

[31] Doyon, S. The many faces of ecstasy. *Current Opinion in Pediatrics* **2001**, *13*, 170-176

[32] Capwell, R. R. Ephedrine-induced mania from an herbal diet supplement. *Am J Psychiatry* **1995**, *152*, 647

[33]Doyle, H.; Kargin, M. Herbal stimulant containing ephedrine has also caused psychosis. *BMJ* **1996**, *313*, 756

[34] Jacobs, K.; Hirsch, K. Psychiatric complications of Ma-huang. *Psychosomatics* **2000**, *41*, 58-62

[35]Emmanuel, N.; Jones, C.; Lydiard, R. Use of herbal products and symptoms of bipolar disorder. *American Journal of Psychiatry* **1998**, *155*, 1627

[36]Martin, W.; Sloan, J.; Sapira, J.; Jasinski, D. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology & Therapeutics* **1971**, *12*, 245-58

[37] Chait, L. Factors influencing the reinforcing and subjective effects of ephedrine in humans. *Psychopharmacology* **1994**, *113*, 381-7

[38] Young, R.; Gabryszuk, M.; Glennon, R. A. (-)Ephedrine and caffeine mutually potentiate one another's amphetamine-like stimulus effects. *Pharmacol Biochem Behav* **1998**, *61*, 169-73

[39]Gruber, A.; Pope, H. G. J. Ephedrine abuse among 36 female weightlifters. *American Journal on Addictions* **1998**, *7*, 256-261

[40] Powell, T.; Hsu, F.; Turk, J.; Hruska, K. Ma-huang strikes again: ephedrine nephrolithiasis. *American Journal of Kidney Diseases* **1998**, *32*, 153-159

[41] Blau, J. Ephedrine nephrolithiasis associated with chronic ephedrine abuse. *Journal of Urology* **1998**, *160*, 825

[42] Nadir, A.; Agrawal, S.; King, P.; Marshall, J. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. *American Journal of Gastroenterology* **1996**, *91*, 1436-8

[43] Borum, M. Fulminant exacerbation of autoimmune hepatitis after the use of ma huang. *American Journal of Gastroenterology* **2001**, *96*, 1654-5

[44] Dowd, J.; Bailey, D.; Moussa, K.; Nair, S.; Doyle, R.; Culpepper-Morgan, J. Ischemic colitis associated with pseudoephedrine: four cases. *American Journal of Gastroenterology* **1999**, *94*, 2430-4

[45] Lichtenstein, G.; Yee, N. Ischemic colitis associated with decongestant use. *Annals of Internal Medicine* **2000**, *132*, 682

[46]Anibarro, B.; Seoane, F. Nonpigmenting fixed exanthema induced by pseudoephedrine. *Allergy* **1998**, *53*, 902-3

[47] Vidal, C.; Prieto, A.; Perez-Carral, C.; Armisen, M. Nonpigmenting fixed drug eruption due to pseudoephedrine. *Annals of Allergy, Asthma, & Immunology* **1998**, *80*, 309-10

[48] Hindioglu, U.; Sahin, S. Nonpigmenting solitary fixed drug eruption caused by pseudoephedrine hydrochloride. *Journal of the American Academy of Dermatology* **1998**, *38*, 499-500

[49] Garcia Ortiz, J.; Terron, M.; Bellido, J. Nonpigmenting fixed exanthema from ephedrine and pseudoephedrine. *Allergy* **1997**, *52*, 229-230

[50] Alanko, K.; Kanerva, L.; Mohell-Talolahti, B.; Jolanki, R.; Estlander, T. Nonpigmented fixed drug eruption from pseudoephedrine. *Journal of the American Academy of Dermatology* **1996**, *35*, 647-8

[51] Sanchez, T.; Sanchez-Perez, J.; Aragues, M.; Garcia-Diaz, A. Flare-up reaction of pseudoephedrine baboon syndrome after positive patch test. *Contact Dermatitis* **2000**, *42*, 312-3

[52] Hauken, M. Fixed drug eruption and pseudoephedrine. *Annals of Internal Medicine* **1994**, *120*, 442

[53]Cavanah, D.; Ballas, Z. Pseudoephedrine reaction presenting as recurrent toxic shock syndrome. *Annals of Internal Medicine* **1993**, *119*, 302-3

[54]Camisa, C. Fixed drug eruption due to pseudoephedrine. *Cutis* **1988**, *41*, 339-40

[55] Sanchez, op. cit.

Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Table 1

Adverse Events using Terminology in AN/AEMS Datafield: "Adverse Event as Reported"	All DS (n)	EADS (n)	nonEA DS (n)	%EA/all DS	%nonEA/ all DS
All adverse events	3308	1398	1910	42.26%	57.74%
Death	137	81	56	59.12%	40.88%
Cardiovascular events					
*heart	397	293	104	73.80%	26.20%
*cardia	146	96	50	65.75%	34.25%
cardiac arrest	18	12	6	66.67%	33.33%
cardiopulmonary arrest	3	2	1	66.67%	33.33%
*any cardiac arrest	21	14	7	66.67%	33.33%
myocardial infarction	23	18	5	78.26%	21.74%
heart attack	29	26	3	89.66%	10.34%
vasospasm	2	1	1	50.00%	50.00%
coronary	6	4	2	66.67%	33.33%
coronary spasm	0	0	0		
heart spasm	1	1	0	100.00%	0.00%
MI/heart attack [any term above]	38	32	6	84.21%	15.79%
chest pain/angina	135	88	47	65.19%	34.81%
MI/heart attack/angina [any term above]	173	120	53	69.36%	30.64%
*tachycardia	78	53	25	67.95%	32.05%
*atria	32	17	15	53.13%	46.88%
*ventricular [cardiac only]	31	22	9	70.97%	29.03%
arrhythmia	20	10	10	50.00%	50.00%
ventricular tachycardia	14	10	4	71.43%	28.57%
atrial fibrillation	28	15	13	53.57%	46.43%
atrial flutter	2	1	1	50.00%	50.00%
irregular heart rate	26	21	5	80.77%	19.23%
PVCs	8	5	3	62.50%	37.50%
*any arrhythmia	98	62	36	63.27%	36.73%
heart pounding	17	14	3	82.35%	17.65%
heart palpitations	174	134	40	77.01%	22.99%
rapid heart	60	45	15	75.00%	25.00%
racing heart	27	25	2	92.59%	7.41%
*other cardiac symptoms	278	218	60	78.42%	21.58%
*hypertens	38	20	18	52.63%	47.37%
*blood pressure [high/low]	137	83	54	60.58%	39.42%
low blood pressure	4	2	2	50.00%	50.00%
hypertension, nonpulmonary	26	13	13	50.00%	50.00%
hypertensive	9	6	3	66.67%	33.33%
high blood pressure	48	34	14	70.83%	29.17%
elevated blood pressure	41	25	16	60.98%	39.02%
increased blood pressure	20	13	7	65.00%	35.00%
any term indicating hypertension	144	91	53	63.19%	36.81%
cerebrovascular accident	2	1	1	50.00%	50.00%
stroke/ brain infarction	60	49	11	81.67%	18.33%
cerebral hemorrhage (ICH)	23	19	4	82.61%	17.39%
transient ischemic attacks	6	4	2	66.67%	33.33%
Stroke/TIA [any above]	91	73	18	80.22%	19.78%
*infarction [any type]	29	24	5	82.76%	17.24%

Sep 06 2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Table 1

Adverse Events using Terminology in AN/AEMS Datafield: "Adverse Event as Reported"	All DS (n)	EADS (n)	nonEA DS (n)	%EA/all DS	%nonEA/ all DS
arterial dissection	4	3	1	75.00%	25.00%
cardiomegaly/enlarged heart	4	2	2	50.00%	50.00%
cardiomyopathy	7	5	2	71.43%	28.57%
*valve	8	3	5	37.50%	62.50%
mitral valve	5	2	3	40.00%	60.00%
valve prolapse	4	2	2	50.00%	50.00%
murmur	1	1	0	100.00%	0.00%
Nervous System					
seizure	121	70	51	57.85%	42.15%
convulsion	5	3	2	60.00%	40.00%
*any convulsion/seizure	126	73	53	57.94%	42.06%
hallucination	24	13	11	54.17%	45.83%
*schizo_	5	3	2	60.00%	40.00%
*psycho_	29	20	9	68.97%	31.03%
*psych_	32	22	10	68.75%	31.25%
psychological	3	2	1	66.67%	33.33%
psychodelic	1	0	1	0.00%	100.00%
mania/manic	18	10	8	55.56%	44.44%
personality change	9	9	0	100.00%	0.00%
depression	53	33	20	62.26%	37.74%
mood swings/changes	38	33	5	86.84%	13.16%
agitation	15	6	9	40.00%	60.00%
*agitat_	28	10	18	35.71%	64.29%
violent	16	5	11	31.25%	68.75%
rage	4	2	2	50.00%	50.00%
anger	4	2	2	50.00%	50.00%
panic attack	20	13	7	65.00%	35.00%
memory loss	22	16	6	72.73%	27.27%
* any mention "mood"	32	30	2	93.75%	6.25%
* any mention "behavior"	32	19	13	59.38%	40.63%
*any mention "emotion"	5	3	2	60.00%	40.00%
incoherent	4	2	2	50.00%	50.00%
confusion	33	15	18	45.45%	54.55%
disorientation	26	16	10	61.54%	38.46%
delirium	3	1	2	33.33%	66.67%
coma [GHB/GBL= 15]	32	4	28	12.50%	87.50%
* any altered consciousness	98	38	60	38.78%	61.22%
* (-) GBL/GHB cases	83	38	45	45.78%	54.22%
vision	59	25	34	42.37%	57.63%
visual	15	5	10	33.33%	66.67%
diplopia	2	1	1	50.00%	50.00%
* any visual distrubance	76	31	45	40.79%	59.21%
addiction	3	1	2	33.33%	66.67%
dependence	2	2	0	100.00%	0.00%
withdrawal	5	3	2	60.00%	40.00%
insomnia	64	45	19	70.31%	29.69%
altered sleep	108	71	37	65.74%	34.26%
*any headache	243	123	120	50.62%	49.38%
migraine headache	8	5	3	62.50%	37.50%
severe headache	35	16	19	45.71%	54.29%
bad headache	6	4	2	66.67%	33.33%
persistent headache	2	1	1	50.00%	50.00%

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Total Number of Adverse Events by Year

	Any Event		
	DS	DR	Total
1997	211	1325	1536
1998	258	851	1109
1999	407	692	1099
Total	876	2868	3744

Number of Adverse Events by Age

Age	Any AE		CV		NS	
(years)	DS	DR	DS	DR	DS	DR
< 19	297	1223	123	540	159	630
19 - 39	490	1495	249	773	264	807
40 - 55	73	138	39	68	40	73
> 55	16	12	5	0	2	5
Total	876	2868	416	1381	465	1515

Percentage of Females by Age

Age	Any AE		CV		NS	
(years)	DS	DR	DS	DR	DS	DR
< 19	68	60	70	60	72	60
19 - 39	62	51	59	52	64	51
40 - 55	65	47	59	14	68	44
> 55	85	50	80	0	100	80

Number of Adverse Events by Year by Major Organ System

	Any Event		CV		NS		GI	
	DS	DR	DS	DR	DS	DR	DS	DR
1997	211	1325	85	635	11	676	70	383
1998	258	851	127	407	142	452	74	251
1999	407	692	204	339	211	387	140	229

AAPC data

ROUTING SLIP
GENERATED BY: HF-40
DATE: SEP 07, 2001

FDA CONTROL NUMBER: 01 4527 **TRACER #:** **OS #:** 0906010118

DATE OF CORRESPONDENCE: 09/05/01 **DATE INTO FDA:** 09/07/01

TO: TOMMY THOMPSON, DEPARTMENT OF HEALTH AND HUMAN SERVICES

FROM: SIDNEY M WOLFE, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

SYNOPSIS: REQUESTS THAT FDA BAN THE PRODUCTION AND SALE OF ALL EPHEDRA-CONTAINING SUPPLEMENTS

LEAD OFFICE: HFA-305 **HOME OFFICE:** HF-40

CONTACT/PHONE#: MIKELE A BRYANT 301-827-4450

COPIES: GENERAL DISTRIBUTION
HF-40 INDYA P GORDON
HF-40 KRISTINE M MORAN
HF-40 LAJUANA D CALDWELL
HF-40 VALERIE A JACKSON WATSON
HF-10 LINDA A SUYDAM
HFS-1

COORDINATION:

SIGNATURE REQUIRED:

REFERRALS FROM HF-40

ASSIGNED TO		ACTION	DUE DATE
HFA-305	BUTLERJ	NECESSARY ACTION	

REMARKS: PLEASE LOG IN THIS PETITION, THANKS!

ROUTING SLIP
GENERATED BY: HF-40
DATE: SEP 07, 2001

FDA CONTROL NUMBER: 01 4527 **TRACER #:** **OS #:** 0906010118

DATE OF CORRESPONDENCE: 09/05/01 **DATE INTO FDA:** 09/07/01

TO: TOMMY THOMPSON, DEPARTMENT OF HEALTH AND HUMAN SERVICES

FROM: SIDNEY M WOLFE, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

SYNOPSIS: REQUESTS THAT FDA BAN THE PRODUCTION AND SALE OF ALL EPHEDRA-CONTAINING SUPPLEMENTS

LEAD OFFICE: HFA-305 **HOME OFFICE:** HF-40

CONTACT/PHONE#: MIKELE A BRYANT 301-827-4450

COPIES: GENERAL DISTRIBUTION
HF-40 INDYA P GORDON
HF-40 KRISTINE M MORAN
HF-40 LAJUANA D CALDWELL
HF-40 VALERIE A JACKSON WATSON
HF-10 LINDA A SUYDAM
HFS-1

COORDINATION:

SIGNATURE REQUIRED:

REFERRALS FROM HF-40

ASSIGNED TO		ACTION	DUE DATE
HFA-305	BUTLERJ	NECESSARY ACTION	

REMARKS: PLEASE LOG IN THIS PETITION, THANKS!

Secretary's Correspondence

DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE SECRETARY
EXECUTIVE SECRETARIAT

From:	**Sidney M. Wolfe**	*OS#:*	**090620010118**
Organization:	**Public Citizen**	*Date on Letter:*	**9/5/01**
City/State:	**Washington DC**	*Date Received:*	**9/6/01**
On Behalf Of:		*Type:*	**General Public**
Subject:	**Request that FDA ban the production and sale of dietary supplements containing ephedrine alkaloids. (Co-signed by Amer Ardati and Ray Woosley).**		

Assigned to:	**FDA**	*Dep.ES:*	**Dick Eisinger**
PC:	**Tom Kuchenberg**	*Date Assigned:*	**9/7/01**
Action Required:	~~**Dep Sec Sig**~~ assigned to Dockets	*Date Reassigned:*	
		Reply Due Date:	~~**9/21/01**~~

Info Copies To:	**ASMB; ASPA; ASPE; DXS; ESS; Kuchenberg, Tom; OGC; SEC**		
Interim (Y/N):	**No**	*Date Interim Sent:*	
Comments:			
File Index:	**po-4-5**	*CCC:*	**Denise Rich**

4527

*** RECEIVED ***
Sep 06,2001 16:17:17 WS# 04
OFFICE OF THE SECRETARY
CORRESPONDENCE
CONTROL CENTER

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

FAX Transmittal Form

To: Tommy Thompson

Number of pages: (including this one)

CC:

From: Sid Wolfe

Date: Refaxed 9/6

Fax Number: 690-7203

Message: