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December 21, 2001

BY HAND

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

Re: **Affirmation of the Safety of Dietary Supplements that Contain Ephedrine Alkaloids, and Refutation of the Citizen Petition Filed by Public Citizen That Seeks an "Imminent Hazard" Declaration Regarding the Sale of Such Products**

Dear Secretary Thompson:

On behalf of our client, Metabolife International, Inc. ("Metabolife"),¹ we hereby submit this response to the above-referenced Citizen Petition filed by Public Citizen on September 5, 2001. In the Citizen Petition, Public Citizen erroneously alleged that dietary supplements containing ephedrine alkaloids present an "imminent hazard" to the public, ignoring the enormous body of scientific evidence supporting the safety and efficacy of this popular category of dietary supplement products. Public Citizen also urged the Department of Health and Human Services ("HHS") to issue an advisory to warn consumers not to use the products, which is clearly unwarranted given the weight of the scientific evidence establishing product safety.

In its Citizen Petition, Public Citizen failed to identify and review the wide array of scientific studies, data, and information in the public domain that supports the safety of dietary supplements that contain ephedrine alkaloids. Numerous well-controlled clinical studies and reports overwhelmingly support the safety profile of ephedrine alkaloids.² In fact, Public Citizen failed to cite the recently released comprehensive science-based risk analysis performed by

¹ Metabolife, which was officially established in 1995, is dedicated to the ethical formulation of dietary supplement products according to sound scientific principles. Metabolife's flagship product, Metabolife 356[®], has in a few years become one of the best selling dietary supplement products in the United States.

² See Studies and Reports that Public Citizen Failed to Cite, Which Support the Safety Profile of Ephedrine Alkaloids. (See Attachment A1).

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Cantox Health Sciences International (the "Cantox Report"),³ which concludes that dietary supplements containing ephedrine alkaloids are safe, when consumed at recommended levels.⁴ In failing to cite these scientific studies and data, Public Citizen clearly did not include representative data and information counter to its position, as required by a Food and Drug Administration ("FDA") regulation, despite the fact that Public Citizen expressly certified that it had supplied all relevant information.⁵ In fact, as explained herein, Public Citizen's claim that these supplements present a hazard to the public, much less an "imminent hazard," is baseless.

Ephedrine alkaloids have been consumed safely worldwide for over 5,000 years, and well-controlled clinical studies and pharmacological data overwhelmingly demonstrate that herbal ephedrine alkaloids, alone or in combination with caffeine, at the servings recommended for most dietary supplements (25 milligrams ("mg")/serving, up to 100 mg/day),⁶ such as in Metabolife 356[®],⁷ are safe.

The adverse side-effects that have been observed in the clinical studies of herbal ephedrine alkaloids or synthetic ephedrine, alone or in combination with caffeine, have been transient and mild, such as dizziness, insomnia, and tremor. Experts have commented that these side-effects "are not much greater in magnitude than the side-effects of caffeine [alone], in quantities that may be consumed in dietary beverages or in [over-the-counter ("OTC")] preparations."⁸ Even FDA has stated that synthetic ephedrine is "generally recognized as safe and effective"

³ Cantox Health Sciences International Report ("Cantox Report"), *Safety Assessment and Determination of Tolerable Upper Limit for Ephedra*, Council for Responsible Nutrition, Dec. 19, 2000, www.crnusa.org/CRNCantoxreport.index.html. (See Attachment A2).

⁴ Indeed, Public Citizen even failed to cite the letter published in the *New England Journal of Medicine*, which called into doubt the conclusions of the Haller/Benowitz analysis, upon which the Citizen Petition heavily relied. See Grover M. Hutchins, *Letter to the Editor of the New England Journal of Medicine*, 344 N. Engl. J. Med. 1095-96 (2001) (critiquing C.A. Haller and N.L. Benowitz, *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedrine Alkaloids*, 343 N. Engl. J. Med. 1833-38 (2000)). (See Attachment A3).

⁵ FDA regulations require a citizen petition to include a certification that the petition "includes representative data and information known to the petitioner which are unfavorable to the petition." 21 C.F.R. § 10.30 (2001).

⁶ See The American Herbal Product Association ("AHPA"), *Ephedra Trade Recommendation*, (Feb. 10, 2000). (See Attachment A4).

⁷ Metabolife 356[®] contains 12 mg of ephedrine alkaloids and 40 mg of caffeine per caplet (up to 24 mg and 80 mg, respectively, per serving) and has a recommended maximum daily dose of 96 mg of ephedrine alkaloids and 320 mg of caffeine alkaloids.

⁸ Graham A. Patrick, Ph.D., R.Ph., *Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids: Summary Conclusions*, Aug. 9, 2000 ("Patrick Summary"). (See Attachment A5).

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("GRASE") at dosages of 150 mg/day in OTC drug products, such as asthma remedies.⁹ Moreover, clinical studies have consistently demonstrated that herbal ephedrine alkaloids or synthetic ephedrine, alone or in combination with caffeine, are safe and efficacious for weight loss when compared to placebo.

Public Citizen's analysis is incomplete, misleading, and contrary to the weight of scientific evidence. The Citizen Petition is primarily based upon adverse event reports ("AERs") that are allegedly associated with ephedrine alkaloids, even though FDA has indicated that AERs cannot be used to establish causation or estimate risk.¹⁰ Moreover, the petition contains no new information. The majority of the information is no different in type or quality than the information that the General Accounting Office ("GAO") has already rejected as providing an insufficient basis for FDA's proposed regulation of ephedrine alkaloids,¹¹ or that which has been widely discredited by experts. Nor is the information any different in type or quality than the information that HHS has historically rejected as being insufficient to establish an "imminent hazard."¹²

In the instant case, the dietary supplement "imminent hazard" provision in the Federal Food, Drug, and Cosmetic Act ("FFDCA")¹³ does not provide HHS with the statutory authority to

⁹ 51 Fed. Reg. 35326, 35331 (Oct. 2, 1986). FDA specifically stated that, in studies, dosages of ephedrine at 25 mg every four hours (150 mg/day) had "little or no effect on the heart beat or blood pressure of adult asthmatics" and adults experienced only mild side-effects, including "tenseness, nervousness, tremor, sleeplessness, loss of appetite, nausea, and difficulty in urination in older males who may have an enlarged prostate gland." *Id.* See 21 C.F.R. § 341.76(d)(1) (2001) (prescribing a dosage limit for ephedrine in bronchodilator drug products of 12.5 to 25 mg every 4 hours, not to exceed 150 milligrams in 24 hours); see also 21 C.F.R. 341.80(d)(1)(ii) (2001) (prescribing a dosage limit for pseudoephedrine (used as a nasal decongestant) of 60 milligrams every four to six hours, not to exceed 240 milligrams/day).

¹⁰ See *The Special Nutritionals Adverse Event Monitoring System*, FDA CFSAN, Office of Special Nutritionals, <http://vm.cfsan.fda.gov/~dms/aems.html> (governing AERs associated with dietary supplements, infant formulas, and medical foods).

¹¹ See generally General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids* (July 1999) ("GAO Report"). (See Attachment A6). Notably, as a result of the GAO's criticism, FDA withdrew many of its initially proposed restrictions. See 65 Fed. Reg. 17474, 17474 (Apr. 3, 2000).

¹² See, e.g., Letter from HHS to James S. Turner, Swankin and Turner, denying a citizen petition seeking a ban on aspartame based upon an "imminent hazard" provision, dated Nov. 21, 1986 ("HHS Aspartame Petition Denial") (finding that over 3,000 AERs allegedly associated with aspartame collected by FDA over a two year period, a review of the AERs performed by a government agency, letters and case studies collected by physicians, and an animal study, even when viewed together, did not establish that aspartame presented an "imminent hazard") (See Attachment A7); see *infra*, discussion in Section II.

¹³ 21 U.S.C. § 342(f)(1)(C) (Supp. 2001); 21 C.F.R. § 2.5 (2001).

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immediately ban ephedrine alkaloids. Public Citizen's claim that the hazards allegedly associated with ephedrine alkaloids are somehow imminent is absurd. FDA has been reviewing the AERs allegedly associated with this issue for eight years; FDA has been actively engaged in the process of seeking out evidence to support the regulation of ephedrine alkaloids for over four years; the Office on Women's Health, in August 2000, held a hearing (the "Ephedra Hearing") to explore all of the relevant evidence on both sides of the debate; and the National Institutes of Health ("NIH") has commissioned a review of the safety and efficacy of ephedra. Despite these efforts, FDA has failed to identify scientific evidence that supports the regulation of dietary supplements containing ephedrine alkaloids, much less the immediate banning of such products. Indeed, in prioritizing issues to address this year, FDA relegated the issue to its "B-List" of priorities, with full knowledge of the information presented in the Citizen Petition.¹⁴ The petition presents no new credible scientific evidence to suggest that ephedrine alkaloids present a hazard, much less one that is imminent.

If HHS granted Public Citizen's request, it would do so in grave error. As noted, an immediate ban is not scientifically supportable or legally justifiable. Moreover, the Surgeon General recently issued a report indicating that "[o]verweight and obesity have reached nationwide epidemic proportions" and that "[b]oth the prevention and treatment of overweight and obesity and their associated health problems are important public health goals."¹⁵ A ban on dietary supplements containing ephedrine alkaloids would deprive millions of Americans of one of the only currently available dietary supplement products that is not only a safe, but an efficacious and inexpensive means of supporting weight loss.¹⁶

Although it is clear that ephedrine alkaloids cannot and should not, be banned, Metabolife strongly supports the promulgation of a reasonable, science-based regulation for ephedrine alkaloids, and looks forward to working with HHS and FDA toward that end. Based on the scientific research described below, Metabolife believes that such a regulation would contain the following requirements, which are consistent (and in some instances even more stringent) with those imposed by the states that have addressed this issue: (a) a dosage limit of 25 mg of ephedrine alkaloids/serving, 100 mg of ephedrine alkaloids/day (commensurate with the requirements in Hawaii, Michigan, Nebraska, Ohio, and Washington); (b) a prohibition on claims

¹⁴ See FY 2001 Center for Food Safety and Applied Nutrition ("CFSA") Program Priorities: Accomplishments Through June 15, 2001 (July 10, 2001) (expressly moving ephedrine alkaloids from the A-List to the B-List).

¹⁵ The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity 2001, HHS, www.surgeongeneral.gov/library. (See Attachment A8).

¹⁶ Ephedra Hearing Transcript ("Tr.") at 139 (George A. Bray, M.D.); George A. Bray, M.D., *Safety of Dietary Supplements Containing Ephedrine Alkaloids*, at 2, 3, and 5 (the "Bray Report") (submitted with testimony at the Ephedra Hearing) (See Attachment A9).

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indicating that consumption of the product helps one to achieve an altered state of consciousness or euphoria, or provides a “legal” alternative for an illicit drug; (c) a detailed mandatory warning to ensure that only appropriate individuals use ephedrine alkaloid and/or ephedrine alkaloid/caffeine dietary supplement products; (d) a prohibition on the sale of ephedrine alkaloids or ephedrine alkaloid/caffeine combinations to minors; (e) a prohibition on the use of synthetic ephedrine alkaloids in dietary supplements; and (f) no prohibition on ephedrine alkaloid/caffeine combinations.

I. The “Imminent Hazard” Standard for Dietary Supplements

Section 402(f)(1)(C) of the FFDCA provides, in pertinent part, that a dietary supplement is adulterated if “the Secretary declares [it] to pose an imminent hazard to public health or safety”¹⁷ Pursuant to this provision, the Secretary cannot delegate this responsibility, and if the Secretary finds that an “imminent hazard” exists, the Secretary must hold a hearing promptly thereafter to affirm or withdraw its initial finding.¹⁸

To provide guidance in interpreting Section 402(f)(1)(C) and the other “imminent hazard” provisions throughout the FFDCA,¹⁹ FDA promulgated a regulation, 21 C.F.R. § 2.5 (2001). According to that regulation, an “imminent hazard” exists if:

[T]he evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health.²⁰

The “number of injuries anticipated and the nature, severity, and duration of the anticipated injury” will also be considered.²¹

¹⁷ 21 U.S.C. § 342(f)(1)(C) (Supp. 2001).

¹⁸ *See id.*

¹⁹ *See, e.g.*, 21 U.S.C. §§ 355(e) (concerning the suspension of a new drug application approval), 360b(e)(1) (concerning the withdrawal of approvals for animal drugs) (Supp. 2001).

²⁰ 21 C.F.R. § 2.5 (2001).

²¹ *See id.* Notably, 21 C.F.R. § 2.5 was enacted prior to Section 4 of the Dietary Supplement Health and Education Act of 1994 (“DSHEA”), Pub. L. No. 103-417 § 4, 108 Stat. 4325 (1994) (codified at 21 U.S.C. § 342(f)(1)(C) (Supp. 2001)), which established the statutory “imminent hazard” provision for dietary supplements. However, FDA made it clear that the regulation’s definition of “imminent hazard” applies to 21 U.S.C. § 342(f)(1)(C), when it decided

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Traditionally, in evaluating whether an "imminent hazard" exists, HHS has considered the following five factors:

- (1) The severity of the harm that could be caused to the public during the completion of customary administrative proceedings;
- (2) The likelihood that the product will cause such harm to consumers while the administrative process is being completed;
- (3) The risk to patients currently taking the product that might be occasioned by the immediate removal of the product, taking into account the other available options and the steps necessary for patients to adjust to the other options;
- (4) The likelihood that, after the customary administrative process is completed, the product will be withdrawn from the general market; and
- (5) The availability of other approaches to protect the public health.²²

II. Historically, HHS Has Interpreted the "Imminent Hazard" Provision Narrowly, and Has Discounted Anecdotal Evidence, Such as AERs, Inapposite Pharmacological/Toxicological Evidence, and Poorly Designed Studies.

In the past, HHS has interpreted the "imminent hazard" provisions in the FFDCA narrowly, first analyzing under prongs 1 and 2 of the test outlined above whether there is sufficient evidence to suggest that an "imminent hazard" in fact exists.²³ To demonstrate that an "imminent hazard"

against repealing 21 C.F.R. § 2.5 in 1997. See 62 Fed. Reg. 39439 (July 23, 1997) ("FDA has decided to retain Sec. 2.5 because the terms "imminent hazard" appear in several provisions of the [FFDCA] and its implementing regulations (see, e.g., section 402(f)(1)(C) of the [FFDCA] (21 U.S.C. 342(f)(1)(C)) (concerning adulteration of dietary supplements) Therefore, to continue providing guidance in interpreting these and other provisions in the [FFDCA] and FDA regulations, the agency is retaining Sec. 2.5").

²² See, e.g., Letter from HHS to Karim Ahmed, Ph.D., Natural Resources Defense Council, Inc., denying a citizen petition seeking to suspend the approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds under an "imminent hazard" provision, dated Nov. 19, 1985 ("HHS Penicillin Petition Denial"), at 5 (See Attachment A10); Letter from HHS to Sidney M. Wolfe, M.D., Health Research Group, denying a citizen petition seeking to ban the use of Feldene (piroxicam) in people over aged 60, dated July 7, 1986 ("HHS Feldene Petition Denial") (affirming FDA's recommendation ("FDA Feldene Recommendation"), at 2) (See Attachment A11).

²³ See, e.g., Letter from HHS to James S. Turner, Swankin and Turner, denying a citizen petition seeking a ban on aspartame based upon an "imminent hazard" provision, dated Nov. 21, 1986 ("HHS Aspartame Petition Denial")

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exists, HHS typically requires petitioners to provide well-controlled human scientific studies, not anecdotal evidence, such as AERs, inapposite theoretical pharmacological/toxicological evidence, or poorly designed studies. Generally, if HHS determines that no "imminent hazard" exists, it does not address the remaining three factors militating against the immediate ban, or it addresses them only in a cursory fashion.²⁴

For example, in 1986, the Community Nutrition Institute ("CNI") filed a petition with the HHS seeking an immediate ban of aspartame, pursuant to an "imminent hazard" provision, which claimed that aspartame causes neurological damage (e.g., seizures) or eye damage in a significant portion of consumers.²⁵ To support that claim, CNI relied primarily on anecdotal data concerning epileptic seizures and eye damage, including over 3,000 AERs allegedly associated with aspartame collected by FDA over a two year period, a review of a portion of the AERs conducted by the Centers for Disease Control ("CDC"), letters and case reports collected by several physicians, and even an animal study.

However, HHS concluded that this information was insufficient to establish that an "imminent hazard" was present, explaining that "[t]he evidence submitted [by the petitioners] is not of the type that, standing in and of itself, establishes a link between aspartame consumption and possible harm to public health."²⁶ HHS further explained that the type of information presented was insufficient to "materially affect the scientific determination that aspartame has been shown to be safe for its approved uses,"²⁷ because the information was not "reliable or concrete."²⁸

In reaching the conclusion that the 3,000 AERs presented did not suggest a causal relationship between aspartame and seizures, HHS noted that the AERs "showed no consistent association

(See Attachment A7); HHS Penicillin Petition Denial (See Attachment A10); HHS Feldene Petition Denial (See Attachment A11).

²⁴ See e.g., HHS Aspartame Petition Denial (not addressing the remaining factors at all) (See Attachment A7); HHS Penicillin Petition Denial, at 11 (addressing the remaining factors in a cursory fashion) (See Attachment A10); HHS Feldene Petition Denial (affirming the FDA Feldene Recommendation) (See Attachment A11); FDA Feldene Recommendation, at 6 (addressing the remaining factors in a cursory fashion) (See Attachment A11).

²⁵ HHS Aspartame Petition Denial, at 1-2. (See Attachment A7).

²⁶ *Id.* at 2. See also FDA Feldene Recommendation, at 5 (recommending the denial of a petition seeking to ban Feldene for use in people over the age of 60. HHS noted that the 2,803 AERs (182 of which involved fatalities) collected over a four year period, in addition to theoretical pharmacokinetic evidence, failed to provide any evidence that the drug presented an "imminent hazard") (See Attachment A11).

²⁷ See HHS Aspartame Petition Denial, at 8 (See Attachment A7).

²⁸ See *id.*

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between the occurrence of seizure and exposure to aspartame containing products.”²⁹ Moreover, HHS noted that in reviewing the anecdotal reports and available medical records, FDA was “unable to eliminate factors other than aspartame consumption as possible causes of reported seizures,” given that “[s]eizure susceptibility can be increased by a number of factors, such as estrogenic activity, insulin deficiency, hydration, hyponatremia, and starvation.”³⁰

HHS also acknowledged that the AERs in and of themselves could not establish a causal relationship between aspartame and seizures, given the high rate of seizures in the general population:

Approximately one percent of the population suffers from seizures. Epilepsy is second only to stroke as the leading neurological disorder in the United States. Under these circumstances and, because aspartame is frequently consumed by large numbers of people, it is not surprising that there may be a chance occurrence of seizure activity following ingestion of aspartame in seizure prone people. In fact, such a happenstance would not be unexpected.³¹

Further, HHS acknowledged that the 3,000 AERs, and other forms of anecdotal evidence, could not even establish a hypersensitivity towards aspartame in certain populations because the symptoms attributed to aspartame were of “a common nature” (e.g., headache).³² According to HHS, the recommendations of the CDC from its analysis of the AERs, and an FDA guidance document,³³ only scientific evidence from well-controlled clinical trials focusing on specific endpoints could establish hypersensitivity to a product.³⁴

Furthermore, HHS dismissed claims that the 152 AERs received by FDA relating to eye damage had any causal relationship to aspartame, noting that (1) the majority of the cases were more likely caused by underlying disease or concurrent drug use, and (2) many of the AERs could not be properly analyzed because of insufficient or absent medical records.³⁵ HHS also determined that toxicological/pharmacological evidence showing that methyl alcohol at high levels could

²⁹ See *id.* at 3.

³⁰ See *id.* at 4.

³¹ *Id.* at 4.

³² See *id.* at 4-5.

³³ See FDA’s Advisory Committee on Hypersensitivity to Food Constituents (May 9, 1986).

³⁴ See HHS Aspartame Petition Denial, at 5 (See Attachment A7).

³⁵ See *id.*

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adversely affect the eyes, was insufficient to demonstrate that aspartame presented an “imminent hazard” because methyl alcohol is present in aspartame only at low levels.³⁶ Finally, HHS also rejected the petitioner’s presentation of an animal study, which allegedly suggested that aspartame may cause eye damage. According to HHS, that study was merely preliminary, and insufficient to link aspartame to eye damage because it was an animal study with multiple design deficiencies.³⁷

HHS’ denial of Public Citizen’s 1986 petition seeking to ban the use of Feldene in people over the age of 60 provides another example of HHS’ steadfast refusal to find that an “imminent hazard” is present based merely upon AERs, other forms of anecdotal evidence, AER analyses, and weak pharmacokinetic evidence, particularly when such evidence is contradicted by well-controlled clinical studies.³⁸ In that case, to support its petition, Public Citizen presented, among other things, 2,803 AERs (182 of which involved fatalities) collected by FDA over a two year period. In denying the petition, HHS discounted the large number of AERs associated with Feldene, in part, because of overreporting (FDA estimated that the reporting rate for adverse events allegedly associated with Feldene was approximately 1.65 times the rate expected).³⁹

III. **The “Imminent Hazard” Provision in the FFDCA for Dietary Supplements Does Not Provide HHS With Authority to Ban Dietary Supplements Containing Ephedrine Alkaloids.**

In the present case, as detailed below, Public Citizen cited no new information to advance its position. Rather, Public Citizen cited 1,398 AERs collected over an eight year period, anecdotal case studies, faulty analyses of the AERs, inapposite analogies to the pharmacological/toxicological properties of other substances, and a handful of faulty or inconsistent studies – all of which have been available for quite some time and most of which have already been discredited by the GAO and/or experts with backgrounds in cardiology, pharmacology, toxicology, pathology, and neurotoxicology. Moreover, the types of evidence cited by Public Citizen here are no different than the types of evidence cited by CNI in the aspartame petition, and that cited by Public Citizen previously in the Feldene petition – all of which HHS has concluded are insufficient to establish an “imminent hazard.”

³⁶ See *id.*

³⁷ See *id.* at 6 (footnote 6).

³⁸ See generally FDA Feldene Recommendation, *aff’d* HHS Feldene Petition Denial (See Attachment A11).

³⁹ See FDA Feldene Recommendation at 4-5, *aff’d* HHS Petition Denial at 1. Notably, although the FDA Feldene Recommendation does not explain how FDA arrived at its estimate of the reporting rate, it does state that it is adjusting the numbers because of an observed trend in adverse event reporting for all drugs and because all drugs have increased reporting rates in the first three years in which they are marketed. See *id.* (See Attachment A11).

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In addition, Public Citizen failed to cite the well-controlled studies, reports, and pharmacological/toxicological data on ephedrine alkaloids, which overwhelmingly support the safety profile of ephedrine alkaloids. Public Citizen's failure to cite the extensive favorable scientific data is contrary to FDA's citizen petition regulation and, indeed, contrary to Public Citizen's own certification that it had supplied all relevant information.⁴⁰ As explained herein, scientific studies, the body of research conducted by Dr. Arne Astrup over the last 20 years, and 5,000 years of consumption all over the world, indicate that the 25 mg serving limit of ephedra, alone or in combination with caffeine, is safe and efficacious in supporting weight loss.⁴¹ Recent supportive studies include: (1) a six month safety and efficacy trial conducted by Harvard and Columbia Universities (abstract),⁴² (2) an eight week trial conducted by Columbia University,⁴³ (3) a three month safety and efficacy trial conducted by Pennington Biomedical Research Center at Louisiana State University (abstract),⁴⁴ (4) a three month safety and efficacy trial conducted by the Department of Human Biology and Nutritional Sciences at the University of Guelph (abstract),⁴⁵ (5) a literature review conducted by Dr. Frank Greenway,⁴⁶ and (6) the Cantox Report,⁴⁷ which reviewed data from 19 clinical trials, the FDA's published AERs, data from animal and human studies, case reports, and published articles, in conducting its safety evaluation. The Cantox risk analysis identified a dosage of 150 mg/day of ephedra (50% higher than the serving limit suggested above) as the lowest level at which moderate adverse effects were first observed, and a dosage of 90 mg/day as the "no observed adverse effect level." Moreover, as mentioned, FDA

⁴⁰ 21 C.F.R. § 10.30 (2001).

⁴¹ See *infra*, discussion in Section III(B).

⁴² See Carol N. Boozer, et al., *Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial (Abstract)*, 9(1) *Obesity Research* 68 (2001) and 15(4) *FASEB Journal* A403 (2001). (See Attachment A12).

⁴³ Carol N. Boozer, et al., *An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-Blind Trial*, 25 *Int'l Journal of Obesity* 316 (2001) (also referred to as Nasser et al. (1999) (meeting abstract)). (See Attachment A13).

⁴⁴ De Jonge, et al., *Safety and Efficacy of an Herbal Dietary Supplement Containing Caffeine and Ephedra for Obesity Treatment*, 9(3) *Journal of Obesity Research (Program Abstract PG20)* (Oct. 7-10, 2001). (See Attachment A14).

⁴⁵ Belfie, et al., *Safety and Effectiveness of an Herbal Dietary Supplement Containing Ephedra (Ma Huang) and Caffeine (Guarana Extract) When Used in Combination With a Supervised Diet and Exercise Intervention*, 9(3) *Journal of Obesity Research (Program Abstract PG26)* (Oct. 7-10, 2001). (See Attachment A15).

⁴⁶ F.L. Greenway, *The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent*, 2 *Obesity Reviews* 199 (2001). (See Attachment A16).

⁴⁷ See generally the Cantox Report. (See Attachment A2).

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itself has issued an OTC drug monograph that authorizes the use of ephedrine at levels of up to 25 mg/serving, and 150 mg/day.⁴⁸

A. In Attempting to Advance Its Position, Public Citizen Cited No New Evidence, and the Evidence Cited Is Not of the Type or Quality That Could Support an "Imminent Hazard" Determination.

As mentioned above, Public Citizen's ephedrine alkaloid petition contains no new information and the information presented is no different in type or quality than the information that HHS has historically rejected as being insufficient to establish an "imminent hazard." In addition, the evidence presented by Public Citizen (e.g., AERs, anecdotal case studies, analyses of AERs, inapposite pharmacological/toxicological data about other substances, and poorly designed studies) is not even the type of evidence that can demonstrate that certain individual groups have a hypersensitivity to ephedrine alkaloids. In accordance with the HHS Aspartame Petition Denial, the CDC's recommendation in that case, and an FDA guidance document, only well-controlled clinical studies with specific endpoints can yield such information.⁴⁹

1. Public Citizen Cannot Establish that Ephedrine Alkaloids Present an "Imminent Hazard" Based on 1,398 AERs Collected Over an Eight Year Period.

Public Citizen cannot establish that ephedrine alkaloids present an "imminent hazard" based on merely 1,398 AERs collected over an eight year period, just as the aspartame petitioners could not demonstrate that aspartame presented an "imminent hazard" with over 3,000 AERs collected over a two year period,⁵⁰ and just as the Feldene petitioners could not do so with 2,803 AERs (which included 182 deaths) collected over a two year period.⁵¹

As an initial matter, the very existence of 1,398 AERs collected over an eight year period is not of particular concern when that number is placed into perspective. In 2000, alone, the American Association of Poison Control Centers ("AAPCC") received 16,649 calls regarding exposure, or potential exposure, to aspirin, and 56,731 calls regarding exposure, or potential exposure, to acetaminophen. After collecting follow-up information on approximately 44% of those calls,

⁴⁸ See 51 Fed. Reg. at 35331; 21 C.F.R. § 341.76(d)(1) (2001).

⁴⁹ See HHS Aspartame Petition Denial, at 5 (See Attachment A7); FDA's Advisory Committee on Hypersensitivity to Food Constituents (May 9, 1986).

⁵⁰ See generally HHS Aspartame Petition Denial. (See Attachment A7).

⁵¹ See FDA Feldene Recommendation at 3. (See Attachment A11).

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trained medical personnel at the poison control centers determined that of the adverse events followed in the year 2000, at least 5,946 adverse events (including 52 deaths) were plausibly related to aspirin and at least 9,660 adverse events (including 99 deaths) were plausibly related to acetaminophen.⁵²

Moreover, it is well-established that reports collected by passive surveillance systems, such as the systems operated by the AAPCC and FDA, cannot prove causation. Indeed, FDA's website posts a disclaimer that cautions that "there is no certainty that a reported adverse event can be attributed to a particular product."⁵³ Further, Dr. Christine Lewis, the Director of FDA's Office of Nutritional Products, Labeling, and Dietary Supplements recently stated that AERs "do not offer proof that any supplement caused the death or illness listed, only that the person ingested the supplement before his or her death or injury."⁵⁴ Even the AAPCC's passive surveillance system, which is more sophisticated than FDA's, is still not capable of, or designed to, make conclusive causation determinations.

The GAO, in reviewing FDA's proposed rule for ephedrine alkaloids, which relied upon the 864 AERs⁵⁵ collected from January 1993 through June 1997 for support, explained why AERs cannot establish causation. According to the GAO, AERs are subjective, imprecise, and fail to consider: (1) that professional opinions as to the causation of adverse events may differ when multiple risk factors are involved, (2) that there are biases inherent in spontaneous reporting, (3) that the quality of the data received is generally poor, (4) an estimation of population exposure, and (5) that serious adverse events are more likely to be spontaneously reported than less serious events, and therefore underreporting leads to skewed data.⁵⁶

Importantly, the GAO criticized the 864 AERs relied on by FDA as being particularly faulty. The GAO observed that at least 45% of these AERs lacked sufficient information on dose,

⁵² The adverse effect numbers listed represent the aggregate number of minor, moderate, and major effects, and deaths reported by the AAPCC. See Toby L. Litovitz, M.D., *2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System*, 19 *The American Journal of Emergency Medicine* 337 (Sept. 2001). (See Attachment A17).

⁵³ See *The Special Nutritionals Adverse Event Monitoring System*, FDA CFSAN, Office of Special Nutritionals, <http://vm.cfsan.fda.gov/~dms/aems.html>.

⁵⁴ Tracy Wheeler & Jim Quinn, *Herbal Products Cause Ill Effects: Natural Remedies Can Prove Deadly*, *Akron Beacon Journal*, May 9, 2000 (citing Christine Lewis). (See Attachment A18).

⁵⁵ See GAO Report at 11. (See Attachment A6).

⁵⁶ See *id.* at 35-36.

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frequency or duration to make any conclusions regarding the adverse event.⁵⁷ Moreover, at least 62% of the AERs did not contain medical records, which are essential in assessing whether the adverse events may have been caused by underlying conditions, or concurrent drug use, rather than the ingestion of ephedrine alkaloids.⁵⁸

Public Citizen's citation of approximately 554 additional AERs, which were collected by FDA after it issued its proposed rule, does nothing more to support Public Citizen's claim that ephedrine alkaloids present an "imminent hazard" to the public. In fact, citing the additional 554 AERs brings attention to the fact that FDA received fewer AERs in the four years since it issued its proposed rule than it received in the four years prior to issuing the rule, despite increased FDA scrutiny, media attention, and sales. Finally, AERs cannot be turned into reliable sources for causation analysis simply by counting more of them (particularly when they still lack vital information).

2. Public Citizen Advanced Its Case No Further By Citing the Analyses of the AERs Than It Did by Citing the AERs Themselves.

Despite HHS' rejection of the CDC's analysis of the AERs cited by CNI in the aspartame petition,⁵⁹ the inherent unreliability of AERs for causation analysis, and the particular problems with the majority of the AERs that are allegedly associated with ephedrine alkaloids, Public Citizen nevertheless attempted to advance its position by citing AER analyses. The analyses cited by Public Citizen, however, one performed by Dr. Christine A. Haller and Dr. Neal L. Benowitz and one performed by Dr. Raymond Woosley, are not new and have been discredited by experts. Indeed, Dr. Haller and Dr. Benowitz have qualified their own study, clarifying that it cannot be used, as Public Citizen uses it, as evidence of causation.⁶⁰

As a general matter, Dr. Judith Jones, a pharmacology expert, has noted, along with the GAO, that professional opinions as to the causation of adverse events frequently differ when multiple risk factors are involved.⁶¹ Dr. Jones has also observed that AER causation determinations are

⁵⁷ See *id.* at 11.

⁵⁸ See *id.*

⁵⁹ See HHS Aspartame Petition Denial at 3-5. (See Attachment A7).

⁶⁰ C.A. Haller and N.L. Benowitz, *Correspondence (Author's Reply)*, 344 N. Engl. J. Med. 1096 (2001). (See Attachment A3).

⁶¹ See Judith Jones, *Review of Cases Describing Events Associated with Exposure to Various Ephedrine Alkaloid-Containing Products*, Sept. 14, 2000 ("Jones Report"), at 23 (See Attachment A19); see also GAO Report at 35-36 (See Attachment A6).

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subject to reviewer biases, particularly when the AERs have significant information gaps, as those involved here.⁶²

Accordingly, given that Dr. Haller, Dr. Benowitz, and Dr. Woosley were hired by FDA to find support for the agency's proposed regulation on ephedrine alkaloids, the resulting analyses should be subject to strict scrutiny. As detailed below, the results of other experts that reviewed the same AER set, including FDA, differed widely from those of Dr. Haller and Dr. Benowitz and Dr. Woosley. Moreover, several experts have discredited both the Haller/Benowitz analysis and the Woosley analysis for flawed reasoning.

a. The Haller/Benowitz Analysis Has Been Widely Discredited.

When Dr. Haller and Dr. Benowitz reviewed 140 AERs for FDA, they found that 62% of the AERs were "definitely," "probably," or "possibly" related to ephedrine alkaloids.⁶³ Of these events, the majority of which involved cardiovascular or central nervous system symptoms, 10 reported a death, and 13 reported a permanent disability. Thus, Dr. Haller and Dr. Benowitz concluded that ephedrine alkaloids may pose a health risk to certain sensitive groups. These conclusions were published last year in the *New England Journal of Medicine*.

As an initial matter, the Haller/Benowitz analysis is insufficient to demonstrate that ephedrine alkaloids may pose a health risk to certain sensitive groups, as Dr. Haller and Dr. Benowitz suggest. As mentioned above, according to the HHS Aspartame Petition Denial and an FDA guidance document, only well-controlled clinical trials with specific endpoints can demonstrate such hypersensitivity.⁶⁴

Moreover, Dr. Haller and Dr. Benowitz's causation determinations in general were quickly discredited by several experts, including Dr. Jones and experts on the Ephedra Education Council Panel ("EEC Panel") with backgrounds in cardiology, pharmacology, toxicology, pathology, and neurotoxicology. The experts on the EEC Panel, as well as FDA itself, reviewed and evaluated the same series of AERs and disagreed on the causality ratings of each individual report. For example, Dr. Haller and Dr. Benowitz found that 62% of the AERs were somehow related to ephedrine alkaloids, whereas Lori Love of FDA reported that FDA found that at least

⁶² See Jones Report at 23. (See Attachment A19).

⁶³ See C.A. Haller and N.L. Benowitz, *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedrine Alkaloids*, 343 N. Engl. J. Med. 1833-38 (2000). (See Attachment A20).

⁶⁴ See HHS Aspartame Petition Denial, at 5 (See Attachment A7); FDA's Advisory Committee on Hypersensitivity to Food Constituents (May 9, 1986).

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55% of the 140 AERs either lacked sufficient information to be evaluated or were simply not related to ephedrine alkaloids.⁶⁵

Further, after reviewing the AERs at issue in the Haller/Benowitz analysis, the EEC experts concluded that there was no association between the serious adverse events reported and ephedrine alkaloid products.⁶⁶ For example, the Haller/Benowitz conclusion that 10 reports of sudden death could be related to ephedrine alkaloids was refuted by Dr. Grover Hutchins and Dr. Steven Karch, two renowned pathologists, who determined that ephedrine alkaloids could not have been a "contributing or causative factor" of sudden death in any of the AERs reviewed.⁶⁷ Dr. Jones believes that Dr. Benowitz's conclusions were erroneous because, among other things, he ranked cases as "probably" related, even if an essential piece of information, such as the time or potency of the last dose, was missing.⁶⁸

Notably, even Dr. Haller and Dr. Benowitz conceded in their paper that: (1) their conclusions based on the AERs do not prove causation,⁶⁹ (2) their conclusions based on the AERs are not consistent with clinical studies on ephedrine, which have shown that ephedrine alkaloids, taken in single dosages of 25 mg to 50 mg have only moderate effects on heart rate and blood pressure,⁷⁰ and (3) that AERs generally are not good indicators of a product's safety (or risk).⁷¹ In addition, subsequent to the release of the paper, in the April 2001 edition of the *New England Journal of Medicine*, Dr. Haller and Dr. Benowitz again conceded that their paper does not "prove causation, nor does it provide quantitative information with regard to risk."⁷²

⁶⁵ Ephedra Hearing Tr. at 33, 49-51 (Lori A. Love, M.D., Ph.D.).

⁶⁶ See, e.g., Open Letter to the Public and the Scientific Community, a Response to a Paper on Ephedra by Haller and Benowitz Released in the *New England Journal of Medicine*, EEC Panel (Dec. 11, 2000). (See Attachment A21).

⁶⁷ See Ephedra Hearing Tr. at 154 (Dr. Steven Karch), 178 (Dr. Grover Hutchins); see also Grover M. Hutchins, *Letter to the Editor of the New England Journal of Medicine*, 344 N. Engl. J. Med. 1095-96 (2001). (See Attachment A3).

⁶⁸ See Jones Report at 15. (See Attachment A19).

⁶⁹ C.A. Haller and N.L. Benowitz, *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedrine Alkaloids*, 343 N. Engl. J. Med. (2000), at 1837. (See Attachment A20).

⁷⁰ See *id.*

⁷¹ See *id.* at 1838.

⁷² C.A. Haller and N.L. Benowitz, *Correspondence (Author's Reply)*, 344 N. Engl. J. Med. 1096 (2001). (See Attachment A3). Notably, Public Citizen failed to cite or reference this letter.

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b. Dr. Woosley's Study Has Also Been Discredited by Experts.

Dr. Woosley's analysis of FDA's 140 AERs has been thoroughly reviewed and critiqued by Dr. Jones, as well as Dr. Sorrel Schwartz, a professor of pharmacology at Georgetown University. According to Dr. Schwartz, Dr. Woosley devised a complex scoring paradigm for the AERs that could not be repeated. Based upon this system, Dr. Woosley gave 86 AERs a score of 5, purportedly indicating that the adverse event reported was generally accepted as a medical consequence of ephedrine, the temporal relationship was appropriate, dechallenge suggested a causal link, and there was information available to exclude alternative hypotheses.⁷³ In doing so, however, Dr. Woosley failed to explain the types of information in each case that led him to give the case a particular score.⁷⁴ Indeed, when Dr. Schwartz attempted to use Dr. Woosley's classification criteria, he could not identify 10 cases, much less 86, that fulfilled Dr. Woosley's criteria for a score of 5.⁷⁵

Dr. Jones also stated that Dr. Woosley's classification system "lack[ed] scientific rigor."⁷⁶ This determination was based on her observations that: (1) Dr. Woosley described the pharmacological effects of ephedrine without reference to the scientific literature,⁷⁷ (2) in his general narrative concerning the cases, he made the assumption that ephedrine is the most likely cause of cardiovascular events, seizures, personality changes, and in some cases sudden death, without reference to scientific literature and without considering other causes,⁷⁸ and (3) he "invoke[d] some speculative notions relating to possible mechanisms for ephedrine's association with sudden death, and hypersensitivity," without citing scientific literature or cases to support his speculations.⁷⁹

⁷³ See Sorrel Schwartz, Ph.D., *Report Concerning Ephedrine in Herbal Preparations*, dated Sept. 27, 2000 (the "Schwartz Report"), at 19. (See Attachment A22).

⁷⁴ See Jones Report at 12-13 (See Attachment A19); See generally Letter to Dockets Management Branch, FDA, from Robert Stark, M.D., F.A.C.P., F.A.C.C., dated September 25, 2000 ("Stark Report") at 11-12. (See Attachment A23). Dr. Stark is a Clinical Assistant Professor of Medicine at the Yale University and has his own cardiology practice.

⁷⁵ See Schwartz Report at 19. (See Attachment A22).

⁷⁶ Jones Report at 13. (See Attachment A19).

⁷⁷ See *id.*

⁷⁸ See *id.*

⁷⁹ *Id.*

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3. The Anecdotal Evidence Cited by Public Citizen Cannot Be Used to Assess Risk Any More than It Can Be Used to Establish Causation.

In addition, Public Citizen's reference to the data collected by the AAPCC, which shows that the number of reports allegedly associated with ephedrine alkaloids from 1997 to 1999 were on the rise, and its references to multiple case studies theorizing that ephedrine alkaloids could have somehow been related to individual adverse events, do not advance Public Citizen's claim that ephedrine alkaloids should be immediately banned. This information is not new and it does nothing to suggest that ephedrine alkaloids present an "imminent hazard" to the public.

a. The Fact that the AAPCC Reports Allegedly Associated with Ephedrine Alkaloids Were on the Rise from 1997 to 1999 Does Not Suggest that Ephedrine Alkaloids Pose an "Imminent Hazard" to the Public.

As an initial matter, the fact that the AAPCC reports allegedly associated with ephedrine alkaloids were on the rise from 1997 to 1999, standing alone, is meaningless.⁸⁰ It is well-established that anecdotal reports are not good indicators of a product's safety or risk.⁸¹ True risk is calculated by dividing the number of confirmed adverse events by the number of individuals exposed to a product, neither of which are available when evaluating anecdotal reports. Moreover, HHS in its denial of the Feldene petition,⁸² in addition to other experts, has observed that over-reporting can skew estimates of the total number of adverse events associated with a product. Significant over-reporting can be caused by media attention, which influences physician and consumer decisions to attribute an event to a particular product.

For example, at the Ephedra Hearing, in August 2000, Dr. Stephen Kimmel, an expert in cardiovascular epidemiology, revealed that from 1993-1999, there were only two reporting spikes associated with ephedrine alkaloids.⁸³ One spike correlated with negative press surrounding the 1994 incidents involving Formula One®, and the other correlated with a 1996 Montel Williams broadcast. Such spikes have led the EEC experts to estimate that at least 10% of adverse events

⁸⁰ Notably, Public Citizen failed to cite or reference the fact that FDA's AERs declined significantly from 1996-1997, despite increased sales.

⁸¹ See Jones Report at 24. (See Attachment A19); see also *The Special Nutritionals Adverse Event Monitoring System*, FDA CFSAN, Office of Special Nutritionals, <http://vm.cfsan.fda.gov/~dms/aems.html>.

⁸² See HHS Feldene Petition Denial at 1 (affirming FDA Feldene Recommendation at 4-5). (See Attachment A11).

⁸³ See Ephedra Hearing Tr. at 127-28 (Dr. Stephen Kimmel); see also Ephedra Education Council: Facts on Ephedra, *Executive Summary of the HHS Ephedra Meeting*, at 7 (charting the spikes in ephedra related AERs following negative media). (See Attachment A24).

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associated with ephedrine alkaloids are reported, compared to a conservative estimate of a 1% reporting rate for other dietary supplements.

In addition, it is important to remember that conservative estimates indicate that approximately 976,466,984 servings of dietary supplements containing ephedrine alkaloids were sold in 1997; 1,751,381,254 servings were sold in 1998; and 3,086,041,072 servings were sold in 1999.⁸⁴ Yet, even with consumption tripling over that three year time period, the number of alleged adverse events has remained very low. In fact, when taking into account the number of servings consumed, the percentage of reported events has actually declined, despite the growth in media attention and public awareness.⁸⁵

b. Public Citizen's Case Studies, Like AERs and Other Forms of Anecdotal Evidence, Cannot be Used to Assess Risk.

As demonstrated by the HHS Aspartame Petition Denial,⁸⁶ the case studies cited by Public Citizen, like AERs and other forms of anecdotal evidence, cannot be used to assess risk, any more than anecdotal evidence can be used to establish causation. Indeed, FDA concedes on its website that AERs "cannot be used to estimate the rate of occurrence [of an adverse event] in a population."⁸⁷ AERs, case studies, and other forms of anecdotal evidence do not provide a control group to assess the baseline risk for the types of adverse events reported. Regulatory actions, including accurate risk assessments and causation determinations, can only be based on sound science, not anecdotal data.

A study conducted by seven medical experts from the EEC Panel illustrates this point. The EEC study compared the background rates of seizure, stroke, and heart attack in ephedrine alkaloid consumers and non-consumers.⁸⁸ Notably, in making this comparison, the EEC experts made a

⁸⁴ See Arthur Andersen LLP, *Ephedra Survey Results: 1995-1999*, prepared for AHPA, dated Apr. 28, 2000. (See Attachment A25).

⁸⁵ See Open Letter to the Public and the Scientific Community, a Response to a Paper on Ephedra by Haller and Benowitz Released in the *New England Journal of Medicine*, EEC Panel (Dec. 11, 2000) at 10 (charting the number of servings of ephedrine alkaloids consumed compared to the number of adverse event reports). (See Attachment A21).

⁸⁶ See HHS Aspartame Petition Denial at 3-6 (rejecting AERs, letters from physicians, and case reports as being insufficient to establish an "imminent hazard"). (See Attachment A7).

⁸⁷ See *The Special Nutritionals Adverse Event Monitoring System*, FDA CFSAN, Office of Special Nutritionals, <http://vm.cfsan.fda.gov/~dms/aems.html>.

⁸⁸ Ephedra Hearing Tr. at 135, 136, 138 (Dr. Stephen Kimmel); see also Stephen Kimmel, *Summary of Incidence of Seizures, Strokes, and Myocardial Infarction in the Population and Estimations of Risk in the Population from Ephedra Products* (See

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series of conservative assumptions, such as gross under-reporting of events associated with ephedrine alkaloids, to fashion a "worst case scenario" such that, if anything, they overestimated the number of serious adverse events in ephedrine alkaloid consumers. The study showed that: (1) the estimated rate of spontaneously occurring seizures for non-consumers is 20-60/100,000, whereas the estimated rate of seizures spontaneously occurring in ephedrine alkaloid consumers is 3.6/100,000; (2) the estimated rate of spontaneously occurring strokes for non-consumers is 3-60/100,000 (depending upon the study), whereas the estimated rate of strokes spontaneously occurring in ephedrine alkaloid consumers is 7.1/100,000; and (3) the estimated rate of spontaneously occurring heart attacks in non-consumers is 5-41/100,000, whereas the estimated rate of spontaneously occurring heart attacks in ephedrine alkaloid consumers is 5.1/100,000. Accordingly, the study demonstrates that consumers of ephedrine alkaloid products experience the same number, or even fewer, serious adverse events, such as seizure, stroke, and heart attack, than non-consumers.⁸⁹ This study, like the statistics regarding the high background rates of stroke and seizure referenced in the HHS Aspartame Petition Denial,⁹⁰ undermines the theories advanced by Public Citizen.

**4. Public Citizen's Presentation of Inapposite Pharmacological/
Toxicological Data Concerning PPA and Amphetamine Does Not
Advance Its Position.**

By referring to the Hemorrhagic Stroke Project, a phenylpropanolamine ("PPA") study, and comparing the chemical structures of synthetic ephedrine to PPA and amphetamine, Public Citizen implied that the pharmacology of synthetic ephedrine suggests that ephedrine alkaloids can potentially cause the type of severe adverse cardiovascular or central nervous system ("CNS") events reported in the AERs.⁹¹ This attempt to obfuscate the issue is not new.

The majority of the literature that FDA used in an attempt to support its proposed restrictions on ephedrine alkaloids involved the reported pharmacokinetic effects of PPA and methamphetamine, not the reported effects of synthetic ephedrine or herbal ephedrine

Attachment A26); Selected Slides Used During the Kimmel Presentation at the Ephedra Hearing (See Attachment A26).

⁸⁹ See Ephedra Hearing Tr. at 131-43 (Dr. Stephen Kimmel); Ephedra Education Council, *Executive Summary of the HHS Ephedra Meeting*, Aug. 8-9, 2000, at 3 (See Attachment A24).

⁹⁰ HHS Aspartame Petition Denial at 4. (See Attachment A7).

⁹¹ Citizen Petition, at 3-4.

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alkaloids.⁹² Similarly, at the Ephedra Hearing, Dr. Fong, Dr. Woosley, and Dr. Ricaurte improperly relied upon the known pharmacokinetic effects of PPA, amphetamine, and/or methamphetamine to make assertions about the potential risks posed by synthetic ephedrine.⁹³ However, Dr. Ricaurte later conceded that his animal studies on methamphetamine and extremely high levels of ephedrine did not provide conclusive or determinative evidence with regard to the safety of extremely high levels of ephedrine in humans.⁹⁴

Public Citizen's comparison of synthetic ephedrine to PPA and amphetamine simply does not demonstrate that ephedrine alkaloids present an "imminent hazard" to the public. As mentioned, in its denial of the aspartame petition, HHS concluded that inapposite toxicological/pharmacological evidence is insufficient to demonstrate that the actual food or drug at issue presents an "imminent hazard" to the public.⁹⁵ For example, in that case, HHS determined that a substance does not present a safety risk, even if it would present a safety risk if it were present in the food or drug at issue in a much higher dose.⁹⁶

In the instant case, HHS should reject Public Citizen's implication that ephedrine alkaloids pose an "imminent hazard" to the public based on comparisons to PPA and amphetamine because such comparisons are simply inapposite. Although PPA, amphetamine, and methamphetamine, like ephedrine, are sympathomimetic amines, they are in fact structurally different from ephedrine and have different effects and potencies.⁹⁷ PPA, for example, is a completely different compound than ephedrine in structure, metabolism, tissue disposition, and excretion,⁹⁸ and PPA causes greater elevation in blood pressure than ephedrine and pseudoephedrine, the predominant

⁹² See Ephedra Hearing Tr. at 154 (Steven B. Karch, M.D., (Cardiac Pathologist), City of San Francisco) (noting that over one half of the literature FDA relied upon for its rule involved PPA, and that the PPA literature bears no relevance to ephedrine because it is a completely different compound).

⁹³ See, e.g., Ephedra Hearing Tr. at 23-24 (Dr. Harry Fong) (comparing ephedrine to PPA and methamphetamine); see *id.* at 80-81 (Dr. Raymond Woosley) (noting that in reviewing the AERs, he took into account all that he had learned about the effects of methamphetamine and PPA); see *id.* at 68-71 (Dr. George Ricaurte).

⁹⁴ See *id.* at 103-04 (Dr. George Ricaurte) ("[What we] don't know as yet is, what are the lowest doses of ephedrine that produce the neurotoxicity in the primate brain. [And, we] don't know whether or not the data in monkeys extrapolates to humans").

⁹⁵ See, e.g., HHS Aspartame Petition Denial, at 6-7. (See Attachment A7).

⁹⁶ See *id.*

⁹⁷ See Ephedra Hearing Tr. at 75 (Dr. Ricaurte).

⁹⁸ See Ephedra Education Council: The Facts on Ephedra, *An Examination of the Literature FDA Used in Evaluating the Physiological and Pharmacological Effects of Ephedrine Alkaloids*, at 1-2 (citing the research efforts of Dr. Steven Karch and Dr. Norbert Page). (See Attachment A27).

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alkaloids in ephedrine alkaloid dietary supplements.⁹⁹ Moreover, at the Ephedra Hearing, Dr. Norbert Page, an expert in toxicology, noted that a recent study showed that most dietary supplements with ephedrine alkaloids do not contain PPA, and the few that do, contain only extremely small amounts (PPA content of 0.2% and 1.8% were observed (Betz 1995)).¹⁰⁰ Notably, as detailed in Section III(B)(2), contrary to Public Citizen's implication, the pharmacology of synthetic ephedrine and the other ephedrine alkaloids actually supports the safety profile of ephedrine alkaloids contained in dietary supplements.

5. Public Citizen's Reference to a Handful of Old Studies Does Not Advance Its Position that Ephedrine Alkaloids Present an "Imminent Hazard."

Public Citizen's reference to a handful of so-called "studies," which have long been available, also failed to establish that ephedrine alkaloids present an "imminent hazard" to the public. The first study, James *et al.* (1998),¹⁰¹ which is more than two years old, is particularly troublesome because it, like the study criticized in the HHS Aspartame Petition Denial,¹⁰² is of poor design and does not advance the purpose of the petitioner. That study involved questionnaires filled out by 54 children (28 children reporting chest pain and 26 children with other complaints). Of the 28 cases reporting chest pain, 7 children tested positive for marijuana use, and 5 children tested positive for ephedrine. Of those who tested positive for ephedrine, one also tested positive for amphetamine and methamphetamine, two reported use of OTC cold remedies, and two had pneumonia or bronchitis, which could have caused the chest pain.

Notably, James *et al.* evaluated only symptomatic individuals, and therefore, it is merely a case study - not a well-controlled clinical study on the effects of ephedrine alkaloids. Moreover, the fact that five children experienced chest pain around the time that they used ephedrine cannot establish a causal relationship between ephedrine alkaloids and chest pain any more than the anecdotal evidence in the AERs, particularly given that underlying disease or concurrent drug use was confirmed as a complicating factor in most of the cases. As an additional matter, this study is irrelevant because the major dietary supplement trade associations do not endorse the use of these products by people under the age of 18; most dietary supplement companies, such as

⁹⁹ See *id.*

¹⁰⁰ See Ephedra Hearing Tr. at 147 (Dr. Norbert Page).

¹⁰¹ L. James, *et al.*, *Sympathomimetic Drug Use in Adolescents Presenting to a Pediatric Emergency Department with Chest Pain*, 36 *Journal of Toxicology - Clinical Toxicology* 321 (1998). (See Attachment A28).

¹⁰² See HHS Aspartame Petition Denial, at 6 (footnote 6 - discounting a poorly designed animal study). (See Attachment A7).

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Metabolife, already warn people under the age of 18 not to use ephedrine alkaloids on the product label; and several states (e.g., Ohio, Michigan, Nebraska, and Texas) already prohibit the sale of ephedrine alkaloid dietary supplements to people under 18.

Another study cited by Public Citizen, Young *et al.* (1998),¹⁰³ is even less useful for Public Citizen's purposes. Not only is it merely a rat study, like the study criticized in the HHS Aspartame Petition Denial,¹⁰⁴ but it also fails to establish that the ephedrine alkaloid/caffeine combination has any adverse effects. It merely establishes that ephedrine and caffeine may have additive stimulus effects, which is consistent with the studies conducted by Dr. Arne Astrup¹⁰⁵ (detailed in Section III(B)(1) herein) that indicate that the combination has additive stimulus effects, but not additive adverse cardiovascular effects.

The other two studies cited, Martin *et al.* (1971)¹⁰⁶ and Chait (1971),¹⁰⁷ also fail to advance Public Citizen's position. According to Public Citizen itself, although a hypothesis emerged out of the Martin study that ephedrine, like amphetamines, might have some abuse potential, this hypothesis was quickly contradicted by the Chait study, which concluded that ephedrine has a less addictive profile than amphetamines. Additionally, in one study, Dr. Astrup noted that "no clinically relevant withdrawal symptoms [were] observed," when a regimen of 60 mg of ephedrine combined with 600 mg of caffeine per day was discontinued after 48-50 weeks, indicating that the ephedrine/caffeine combination is not addictive.¹⁰⁸

¹⁰³ See Young, *et al.*, (-) *Ephedrine and Caffeine Mutually Potentiate One and Another's Amphetamine-Like Stimulus Effect*, 61 *Pharmacology, Biochemistry, and Behavior* 169 (1998). (See Attachment A29).

¹⁰⁴ See HHS Aspartame Petition Denial, at 6. (See Attachment A7).

¹⁰⁵ See, e.g., A. Astrup, *et al.*, *The Effect and Safety of an Ephedrine/Caffeine Compound Compared to Ephedrine, Caffeine, and Placebo in Obese Subjects on an Energy Restricted Diet: A Double Blind Trial*, 16 *Int'l Journal of Obesity* 269 (1992) (See Attachment A30); see also S. Toubro, *et al.*, *Safety and Efficacy of Long-Term Treatment with Ephedrine, Caffeine, and Ephedrine/Caffeine Mixture*, 17 (1 Supp.) *Int'l Journal of Obesity* S69 (1993) (See Attachment A31).

¹⁰⁶ W. Martin, *et al.*, *Physiologic, Subjective, and Behavioral Effects of Amphetamine, Methamphetamine, Ephedrine, Phenmetrazine, and Methylphenidate in Man*, 12 *Clinical Pharmacology and Therapeutics*, 245 (1971). (See Attachment A32). This study is anything but new and was thoroughly discussed at the Ephedra Hearing by Dr. Ricaurte, one of FDA's experts. See Ephedra Hearing Tr. at 69 (Dr. Ricaurte).

¹⁰⁷ See L. Chait, *Factors Influencing the Reinforcing and Subjective Effects of Ephedrine in Humans*, 113 *Psychopharmacology* 381 (1994). (See Attachment A33).

¹⁰⁸ See S. Toubro *et al.*, *The Acute and Chronic Effects of Ephedrine/Caffeine Mixtures on Energy Expenditure and Glucose Metabolism In Humans*, 17 (3 Supp.) *Int'l Journal of Obesity and Related Metabolic Disorders* S73 (1993). (See Attachment A34).

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Accordingly, even the "studies" that Public Citizen cited do not constitute the type or quality of evidence that could establish an "imminent hazard," even for hypersensitive populations.¹⁰⁹ Moreover, as amply demonstrated in Section III(B), herein, the weight of scientific evidence overwhelmingly supports the safety profile of ephedrine alkaloids.

B. Public Citizen Failed to Cite Relevant Favorable Clinical Studies, the Cantox Report, and Pharmacological Evidence Supporting the Safety Profile of Ephedrine Alkaloids, In Violation of FDA's Citizen Petition Regulation.

As mentioned, Public Citizen failed to cite numerous well-controlled clinical trials involving ephedrine alkaloids, as well as the Cantox Report, a comprehensive science-based risk analysis that is based upon clinical studies and scientific literature associated with ephedrine alkaloids. In omitting this evidence, Public Citizen failed to follow FDA's regulation governing citizen petitions, which requires the petition to provide all relevant information, including that "which is unfavorable to the petitioner's position."¹¹⁰

As detailed below, the Cantox Report, which was released in December 2000, concluded that dietary supplements containing ephedrine alkaloids, when taken at the dosage levels recommended by industry, are safe. The Cantox Report relied on 19 controlled human clinical trials, including a recent Harvard/Columbia study conducted by Dr. Carol Boozer¹¹¹ and Dr. Patricia Daly,¹¹² one of the few studies on the long-term effects of an herbal combination of ephedrine alkaloids/caffeine alkaloids. Other core research includes, an 8-week study on Metabolife 356[®] (an herbal combination of ephedrine alkaloids/caffeine alkaloids), conducted by Dr. Boozer, and the body of research on synthetic ephedrine¹¹³ and synthetic ephedrine/caffeine combinations conducted by Dr. Arne Astrup,¹¹⁴ who has been an authority in the field for 20 years and has conducted clinical trials on over 200 subjects.

¹⁰⁹ See HHS Aspartame Petition Denial, at 5 (See Attachment A7); FDA's Advisory Committee on Hypersensitivity to Food Constituents (May 9, 1986).

¹¹⁰ 21 C.F.R. § 10.30 (2001).

¹¹¹ Dr. Boozer is the director of the New York Obesity Research, at St. Luke's-Roosevelt Hospital and Columbia University.

¹¹² Dr. Daly is an endocrinologist and was a professor at Beth Israel Medical Center, at Harvard Medical School when the Harvard/Columbia study was conducted.

¹¹³ The Cantox Report found that synthetic ephedrine studies can be used as a surrogate for herbal ephedrine alkaloid studies. See Cantox Report, Executive Overview, at iv. (See Attachment A2).

¹¹⁴ Based upon his studies, Dr. Astrup has concluded that ephedrine alone, or in combination with caffeine, is safe and efficacious in supporting weight loss. See Arne Astrup, M.D., Ph.D., *Video Testimony for the USDHS Public Hearing*

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These studies, several of which are also summarized below, demonstrate that herbal ephedrine alkaloids in combination with caffeine are efficacious in supporting weight loss, and that the potential side-effects are mild and transient, such as insomnia, dizziness, and tremor. The results of the studies on the herbal combination are consistent with the body of research conducted by Dr. Astrup, and others, on synthetic ephedrine alone, and in combination with caffeine.

Although the clinical studies and reports on herbal ephedrine alkaloids/synthetic ephedrine that support the safety and efficacy profile of herbal ephedrine alkaloids are too numerous to discuss individually, Attachment A1 lists many of them to demonstrate the egregious nature of Public Citizen's omission. Notably, all of the abstracts and reports listed are publicly available on the internet or in FDA's administrative docket for its proposed regulation on ephedrine alkaloids.

1. The Cantox Report Concluded that Ephedrine Alkaloids, at the Level Recommended by the Dietary Supplement Industry, Are Safe.

The purpose of the Cantox Report was to critically review information related to the safety of ephedrine alkaloids. The information reviewed included the scientific literature on herbal ephedrine alkaloids and synthetic ephedrine (recognizing and taking into account the differences and similarities between the two), including clinical studies, toxicology studies, animal studies, published case reports, and AERs (such as the case reports and AERs cited by Public Citizen).¹¹⁵ Notably, Cantox also reviewed and took into consideration clinical studies concerning combination products, such as those containing herbal ephedrine alkaloids or synthetic ephedrine and caffeine. The focus of the assessment was on well-controlled human studies - as they provide the most reliable evidence.¹¹⁶

Using this information, Cantox calculated a "no observed adverse effect level" of 90 mg/day and a "lowest observed adverse effect level" of 150 mg/day.¹¹⁷ The "no observed adverse effect

Meeting: Safety of Dietary Supplements Containing Ephedrine Alkaloids, Aug. 8-9, 2000 ("Astrup Testimony"). (See Attachment A35). Dr. Astrup's studies have demonstrated that ephedrine in combination with caffeine has an additive thermogenic effect, which makes the combination much more efficacious in supporting weight loss than ephedrine alone. *See id.* However, Dr. Astrup has concluded that the combination does not have an additive effect with respect to side-effects. *See id.* The combination does not increase the severity or likelihood of the mild and transient side-effects observed with ephedrine alone (e.g., insomnia, dizziness, tremor, and a slight increase in heart beat). *See id.* In fact, Dr. Astrup has observed that, to the contrary, the ephedrine/caffeine combination cancels out the slight heart rate increase occasionally observed when ephedrine is used alone. *See id.*

¹¹⁵ See Cantox Report, Executive Overview, at iv-x. (See Attachment A2).

¹¹⁶ See Cantox Report, Abstract, at i. (See Attachment A2).

¹¹⁷ See Cantox Report at 158-60. (See Attachment A2).

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level” is the level at which the studies reported no statistically significant increase in the frequency of adverse effects compared to placebo.¹¹⁸ The “lowest observed adverse effect level” is the level at which the studies showed a slight statistical difference, but no significant difference, in the frequency of adverse effects compared to placebo.¹¹⁹

Importantly, the “lowest observed adverse effect level” of 150 mg/day, is 50% higher than the maximum daily dose of ephedrine alkaloids recommended by industry (100 mg/day), and even at that level, no life-threatening or debilitating effects were observed.¹²⁰ The adverse effects observed at that level (e.g., dry mouth, agitation, insomnia, headache, weakness, palpitation, tremor, giddiness, and constipation) were only moderate in intensity and did not persist throughout the studies. Notably, Cantox’s observations regarding the mild nature of the side-effects of ephedrine at 150 mg/day are consistent with those of FDA in the preamble to the monograph for asthma products containing ephedrine.¹²¹

Given that Cantox concluded that all of the relevant scientific data indicates that dietary supplements containing ephedrine alkaloids are safe at dosages of 90 mg/day and 150 mg/day, it is clear that the maximum daily dose recommended by industry of 100 mg/day is appropriate.

Summaries of several reports and abstracts reviewed in the Cantox Report follow:

- **Harvard/Columbia 6-Month Safety and Efficacy Trial¹²²** - This study involved 167 mildly to severely overweight patients ranging in age from 18 to 80. For a six month period, each of the patients was given either a placebo or a combination of 90 mg/day of herbal ephedrine alkaloids and 192 mg/day of herbal caffeine alkaloids, in three divided doses. The study abstract revealed that the treated group lost more body weight and fat than the placebo group. Side-effects in both groups were similar, but the treated group had a slightly higher incidence of dry mouth, insomnia, heartburn, and diarrhea. Although the abstract reported that there was a small, but transient, increase in blood pressure and a small increase in heart rate (approximately four beats per minute) in the treated group, the ephedrine/caffeine combination did not increase heart irregularities. Notably, none of the subjects in the study

¹¹⁸ See *id.* at 158.

¹¹⁹ See *id.* at 160.

¹²⁰ See *id.*

¹²¹ See 51 Fed. Reg. at 35331 (setting a dosage limit of 150 mg/day of ephedrine); see *supra* at note 9.

¹²² Carol N. Boozer, *et al.*, *Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial (Abstract)*, 9(1) *Obesity Research* 68 (2001) and 15(4) *FASEB Journal* A403 (2001). Although abstracts of this study have been released, the study has not yet been published in its entirety. (See Attachment A12).

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suffered from life-threatening events. In a recent interview, Dr. Boozer, one of the investigators in the study, reported that, with respect to the treated group, they "didn't see any significant adverse events,"¹²³ such as seizure, stroke, or myocardial infarction. In another interview, Dr. Daly, the other investigator, added that "[c]ardiovascularly [they] saw nothing of significance."¹²⁴

- **8-Week Columbia Study**¹²⁵ - The 8-Week Columbia Study involved 67 patients ranging in age from 25 to 65. For an 8-week period, each subject was given either a placebo or Metabolife 356® (72 mg/day of herbal ephedrine alkaloids and 240 mg/day of herbal caffeine alkaloids, in three divided doses). The patients in the treated group lost an average of 8.7 pounds during the trial, whereas the patients in the placebo group lost an average of 1.8 pounds. In the treated group, heart rate increased over baseline by 6.9 beats per minute, whereas in the placebo group heart rate decreased by 1.7 beats per minute. The mean systolic and diastolic blood pressure did not differ at the end of the study from the baseline readings in either group. None of the subjects experienced any serious or long-lasting side-effects during the trial. Self-reported transient side-effects in both groups that completed the study were similar, except that the treated group had a slightly higher incidence of dry mouth and insomnia.
- **Astrup - Effects of Ephedrine Alone**¹²⁶ - In one study, Dr. Astrup and his team of researchers examined the immediate effect of single doses of synthetic ephedrine at three different levels (10, 20, and 40 mg) in six healthy adults (at least 3 days elapsed between consecutive tests). In that study, Dr. Astrup observed that ephedrine has a thermogenic effect, which indicates that it is efficacious in supporting weight loss. In an additional, related study, Dr. Astrup also demonstrated that ephedrine is safe. The 20 mg dose of ephedrine increased heart rate by approximately 4 beats per minute,¹²⁷ and the 40 mg dose of ephedrine

¹²³ *Health Journal: Ephedra Use Grows, But Some Question Its Safety for Dieters*, The Wall Street Journal (Apr. 6, 2001). (See Attachment A36).

¹²⁴ *Ephedra Makers Submit New Data to U.S. FDA*, Reuters English News Service (Dec. 20, 2000). (See Attachment A37).

¹²⁵ Carol N. Boozer, et al., *An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-Blind Trial*, 25 *Int'l Journal of Obesity* 316 (2001) (also referred to as Nasser et al. (1999)). (See Attachment A13).

¹²⁶ A. Astrup et al., *Thermogenic Synergism Between Ephedrine and Caffeine in Healthy Volunteers: A Double-Blind, Placebo-Controlled Study*, 40(3) *Metabolism* 323 (1991) (See Attachment A38); see also A. Astrup et al., *Thermogenic, Metabolic, and Cardiovascular Effects of a Sympathomimetic Agent, Ephedrine, a Double-Blind Placebo-Controlled Study*, 48 *Current Therapeutic Research* 1087 (Dec. 6, 1990) (focusing on different aspects of the same study) (See Attachment A39).

¹²⁷ See A. Astrup et al., *Thermogenic Synergism Between Ephedrine and Caffeine in Healthy Volunteers: A Double-Blind, Placebo-Controlled Study*, 40(3) *Metabolism* 323 (1991). (See Attachment A38).

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only increased the heart rate by 7 beats/minute;¹²⁸ none of the doses of ephedrine had statistically significant effects on arterial blood pressure;¹²⁹ and there were no statistically significant differences between the side-effects reported for any of the doses of ephedrine when compared to placebo.¹³⁰

- **Astrup - Effects of the Ephedrine/Caffeine Combination, Ephedrine Alone, and Caffeine Alone**¹³¹ - In a large double-blind, placebo controlled, randomized human clinical trial, involving 180 obese subjects on a restricted diet, Dr. Astrup examined the effects of a synthetic ephedrine/caffeine combination (20 mg of ephedrine/200 mg of caffeine), synthetic ephedrine (20 mg), caffeine (200 mg), or placebo, each administered 3 times a day for 24 weeks (*i.e.* there were four groups, one ingested the ephedrine/caffeine combination, one ephedrine alone, one caffeine alone, and one placebo alone). In that study, the weight loss in the subjects in the ephedrine/caffeine and ephedrine groups was significantly greater than that in the placebo group from weeks 8-24. The subjects treated with the ephedrine/caffeine combination, for example, lost an average of 17.5% of their body weight, compared to a loss of about 14% for placebo. The side-effects reported in the three treated groups (*i.e.* all groups other than the placebo group), such as tremor, insomnia, and dizziness, were not significantly different from each other. Moreover, the side-effects in all three treated groups were transient and after eight weeks had reached placebo levels. Although there was a slight increase in heart rate observed in the group taking ephedrine alone, the heart rate in the group taking the ephedrine/caffeine combination fell below baseline, demonstrating a positive synergy between the two.

¹²⁸ See A. Astrup *et al.*, *Thermogenic, Metabolic, and Cardiovascular Effects of a Sympathomimetic Agent, Ephedrine, a Double-Blind Placebo-Controlled Study*, 48 *Current Therapeutic Research* 1087 (Dec. 6, 1990). (See Attachment A39).

¹²⁹ A. Astrup *et al.*, *Thermogenic Synergism Between Ephedrine and Caffeine in Healthy Volunteers: A Double-Blind, Placebo-Controlled Study*, 40(3) *Metabolism* 323 (1991) (See Attachment A38); see also A. Astrup *et al.*, *Thermogenic, Metabolic, and Cardiovascular Effects of a Sympathomimetic Agent, Ephedrine, a Double-Blind Placebo-Controlled Study*, 48 *Current Therapeutic Research* 1087 (Dec. 6, 1990) (See Attachment A39).

¹³⁰ See A. Astrup *et al.*, *Thermogenic, Metabolic, and Cardiovascular Effects of a Sympathomimetic Agent, Ephedrine, a Double-Blind Placebo-Controlled Study*, 48 *Current Therapeutic Research* 1087 (Dec. 6, 1990). (See Attachment A39).

¹³¹ A. Astrup, *et al.*, *The Effect and Safety of an Ephedrine/Caffeine Compound Compared to Ephedrine, Caffeine, and Placebo in Obese Subjects on an Energy Restricted Diet: A Double Blind Trial*, 16 *Int'l Journal of Obesity* 269 (1992) (See Attachment A30); see also S. Toubro, *et al.*, *Safety and Efficacy of Long-Term Treatment with Ephedrine, Caffeine, and Ephedrine/Caffeine Mixture*, 17 (1 Supp.) *Int'l Journal of Obesity* S69 (1993) (Dr. Toubro is one of Dr. Astrup's colleagues and these articles discuss the results of the same study) (See Attachment A31).

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- **Astrup - Long-Term (48-50 Weeks) Effects of the Ephedrine/Caffeine Combination**¹³²
- As a continuation of the 24-week study, summarized above, Dr. Astrup's researchers gave 127 of the original patients synthetic ephedrine/caffeine combinations (20 mg of ephedrine/200 mg of caffeine) three times a day for an additional 24-26 weeks (for a total of 48-50 weeks). Based on that study, Dr. Astrup concluded that "the ephedrine/caffeine combination is safe and effective in long-term treatment in improving and maintaining weight loss. The side-effects are minor and transient and no clinically relevant withdrawal symptoms have been observed."
- **Daly - Short-Term (8 Weeks) and Long-Term (2 Years) Effects of the Combination of Aspirin, Ephedrine, and Caffeine** - In a study performed by a team of researchers from Harvard Medical School, the safety and efficacy of an aspirin/caffeine/ephedrine combination, in divided, pre-meal doses, was tested in 24 obese humans in a randomized, double-blind, placebo-controlled trial over a period of 8 weeks. The dosages contained 330 mg of aspirin, 150 mg of caffeine, and 75-150 mg of ephedrine (correlated with body weight) per day. Six subjects continued on the aspirin/caffeine/ephedrine mixture for 7 to 26 months (over two years). "In all studies, no significant changes in heart rate, blood pressure, blood glucose, insulin, and cholesterol levels, and no differences in the frequency of side effects were found. [Aspirin/caffeine/ephedrine] in these doses is thus well tolerated in otherwise healthy obese subjects, and supports modest, sustained weight loss even without prescribed caloric restriction, and may be more effective in conjunction with restriction of energy intake."¹³³

Notably, Dr. Frank Greenway, an obesity expert, and Dr. Robert Stark,¹³⁴ a cardiology expert, who have also reviewed the relevant clinical studies and scientific literature, agree with Cantox that ephedrine alkaloids in dietary supplements are safe at recommended dosages. Dr. Greenway, in his recently published literature review, stated that the studies and the literature indicate that ephedrine alone, or in combination with caffeine, is safe and efficacious in supporting weight loss.¹³⁵ In reaching this conclusion, Dr. Greenway noted that the side-effects of caffeine and

¹³² S. Toubro et al., *The Acute and Chronic Effects of Ephedrine/Caffeine Mixtures on Energy Expenditure and Glucose Metabolism In Humans*, 17 (3 Supp.) *Int'l Journal of Obesity and Related Metabolic Disorders* S73 (1993). (See Attachment A34).

¹³³ P.A. Daly et al., *Ephedrine, Caffeine, and Aspirin: Safety and Efficacy for Treatment of Human Obesity*, 17 (1 Supp.) *Int'l Journal of Obesity* S73 (1993) (emphasis added). (See Attachment A40).

¹³⁴ Dr. Stark is a Clinical Assistant Professor of Medicine at the Yale University and has his own cardiology practice.

¹³⁵ See F.L. Greenway, *The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent*, 2 *Obesity Reviews* 199, 208 (2001) (See Attachment A16).

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ephedrine, even at "acute dosing are mild and transient."¹³⁶ According to Dr. Greenway, "[o]besity is chronic, requires chronic treatment, its incidence is increasing and it has few effective treatments. The benefits of caffeine and ephedrine in treating obesity appear to outweigh the small associated risks."¹³⁷ More recently, Dr. Greenway stated that the new studies that have been conducted on actual dietary supplements, such as the 8-Week Columbia Study, alleviate concerns that other ingredients in dietary supplements containing ephedrine alkaloids and caffeine interact adversely with those ingredients. According to Dr. Greenway, "these [new] clinical trials of products containing herbal caffeine and ephedra with or without other herbs show safety and efficacy similar to trials of pharmaceutical grade caffeine and ephedrine."¹³⁸

In addition, Dr. Stark noted that the ranges of dosages of ephedrine and/or caffeine tested in the majority of the studies are effectively equivalent to the dosages of herbal ephedrine alkaloids and/or caffeine in the leading dietary supplement products.¹³⁹ (Notably, in certain studies, such as the Daly study described above, the dosage of ephedrine (150 mg/day) even exceeds the maximum daily dosage recommended by industry (100 mg/day)). Accordingly, Dr. Stark concluded that "there is no causal link between the doses of [ephedrine alkaloids and caffeine] recommended by the industry and serious adverse events."¹⁴⁰

Since the issuance of the Cantox Report, two new abstracts of studies have been published in the proceedings of the North American Association for the Study of Obesity's October 7-10, 2001, Annual Meeting. These include:

- **De Jonge - 3 Month Caffeine/Herbal Ephedrine Alkaloid Safety and Efficacy Trial** - This three month, double-blind clinical trial compared a combination of caffeine and herbal ephedrine alkaloids (70 mg of caffeine alkaloids and 24 mg of ephedrine alkaloids three times per day) to placebo. The researchers concluded that the group taking caffeine and ephedra increased their metabolic rate and lost more weight than the placebo group safely. The treated group lost an average of approximately 8.8 pounds during the trial, whereas the patients in the placebo group lost an average of approximately 1.5 pounds.¹⁴¹

¹³⁶ *Id.* at 199 (summary). (See Attachment A15).

¹³⁷ *Id.*

¹³⁸ See Letter from Frank Greenway, M.D. to Paul D. Rubin, dated November 20, 2001. (See Attachment A16).

¹³⁹ See Letter from Robert M. Stark, M.D., F.A.C.P., F.A.C.C., to the Office on Women's Health, dated Aug. 8, 2000 ("Stark Summary") at 1. (See Attachment A23).

¹⁴⁰ *Id.*

¹⁴¹ De Jonge, *et. al.*, *Safety and Efficacy of an Herbal Dietary Supplement Containing Caffeine and Ephedra for Obesity Treatment*, 9(3) *Journal of Obesity Research* (Program Abstract PG20) (Oct. 7-10, 2001). (See Attachment A14).

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- **Belfie – Belfie 3 Month Caffeine/Herbal Ephedrine Alkaloid Safety and Efficacy Trial** - This three month, double-blind clinical trial compared ephedra (20 mg ephedrine alkaloids) and guarana (200 mg caffeine), taken three times daily, to a placebo. Although the results did not support adipose mass reduction, the researchers concluded that the benefits of the caffeine/herbal ephedrine alkaloid supplement were likely due to anorectic effects and that the product “had only mild side effects when taken in a controlled manner.”¹⁴²

These new studies only provide further strong support for the conclusions of the Cantox Report regarding the safety of ephedrine alkaloid/caffeine supplement products.

2. The Results of the Cantox Report and the Clinical Studies Are Consistent with the Known Pharmacology of Ephedrine Alkaloids.

The ephedrine alkaloids in most commercially available ephedra plants include: ephedrine, pseudoephedrine, methylephedrine, methylpseudoephedrine, norpseudoephedrine, and norephedrine.¹⁴³ The predominant alkaloid is ephedrine, which usually comprises between 40-90% of the total alkaloids in the plant.¹⁴⁴ In general, all the alkaloids in ephedra have similar biological effects on the cardiovascular system and central nervous system (“CNS”), but not to the same degree.¹⁴⁵ For example, pseudoephedrine, the second most predominant alkaloid (present in ephedra in anywhere from a 5:1 to 2:1 ratio with ephedrine), is less potent than ephedrine.¹⁴⁶ However, because ephedrine is the predominant alkaloid in ephedra, it is well-recognized that ephedrine is a good indicator of the pharmacology and toxicology of ephedra.¹⁴⁷

Furthermore, because pseudoephedrine is less potent than ephedrine, and because herbal ephedra is believed to be absorbed more slowly than ephedrine, the herbal ephedrine alkaloids in dietary supplements are likely to be safer on a milligram per milligram basis than synthetic

¹⁴² Belfie, et. al, *Safety and Effectiveness of an Herbal Dietary Supplement Containing Ephedra (Ma Huang) and Caffeine (Guarana Extract) When Used in Combination With a Supervised Diet and Exercise Intervention*, 9(3) *Journal of Obesity Research* (Program Abstract PG26) (Oct. 7-10, 2001). (See Attachment A15).

¹⁴³ See Cantox Report, Executive Overview at iii. (See Attachment A2).

¹⁴⁴ See *id.*

¹⁴⁵ See *id.*

¹⁴⁶ See *id.*

¹⁴⁷ See *id.* at iv, vi.

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ephedrine.¹⁴⁸ Thus, risk assessments based upon synthetic ephedrine as a surrogate for ephedra, or herbal ephedrine alkaloids, provides a conservative evaluation of the safety profile of the herb.¹⁴⁹

According to Dr. Graham A. Patrick,¹⁵⁰ a pharmacology/toxicology expert, the biological effects of ephedrine enable it to treat nasal congestion, to treat asthma, to treat shock, to control the appetite, and to increase energy.¹⁵¹ However, as shown by the studies and scientific literature presented above, ephedrine at recommended levels, potentially, can also cause transient and mild negative side-effects, such as increased systolic blood pressure, increased heart rate, urinary retention, constipation, nervousness, dizziness, insomnia, anorexia, and tremor.¹⁵² Nevertheless, after reviewing the clinical studies and relevant scientific literature on the matter, Dr. Patrick observed that to the extent that side-effects occur when herbal ephedrine alkaloids/synthetic ephedrine is taken as directed, alone or in combination with caffeine, they are not much greater in magnitude than the side-effects of caffeine in quantities that may be consumed in dietary beverages or in OTC caffeine preparations.¹⁵³

Indeed, after reviewing the same studies and relevant literature, Dr. Stark concluded that the overall health risk associated with ephedrine alkaloids taken at the recommended dosages, even when combined with caffeine, is far less than that associated with ingestion of peanut products by the general population, a small percentage of whom have peanut allergies.¹⁵⁴

In addition, Dr. Patrick noted that the risk of experiencing adverse events from using dietary supplements containing ephedrine alkaloids should not increase with long-term use.¹⁵⁵ Absorption of ephedrine begins within minutes after ingestion, and the peak concentration in the plasma is obtained within 1 to 2 hours. The half-life of ephedrine ranges from 4-6 hours.

¹⁴⁸ See *id.* at ii; see also Report of Graham A. Patrick, Ph.D., R.Ph., dated Sept. 27, 2000 ("Patrick Report") at 2. (See Attachment A5).

¹⁴⁹ See Cantox Report, Executive Overview at iv. (See Attachment A2).

¹⁵⁰ Graham A. Patrick, Ph.D., R.Ph., is a Professor of Pharmacology and Toxicology at the Virginia Commonwealth University, Medical College of Virginia.

¹⁵¹ See Patrick Summary at 1. (See Attachment A5).

¹⁵² See *id.*

¹⁵³ See *id.* at 1, 3.

¹⁵⁴ Stark Summary at 3. (See Attachment A23).

¹⁵⁵ See Graham A. Patrick, Ph.D., R.Ph., *Preliminary Commentary on Food and Drug Administration Proposed Rule on Limitations on Dietary Supplements Containing Ephedrine Alkaloids*, 1997 ("Patrick 1997 Comments") at 2-3. (See Attachment A5).

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Because the maximum accumulation (the plateau level) of a compound is generally achieved within 5 to 7 half-lives, ephedrine reaches its maximum level in the blood between 1 and 4 days of taking it on a regular schedule. There is no increased accumulation of ephedrine in the plasma beyond that, even though dosing continues at a steady rate. Accordingly, the level of ephedrine in the plasma after 7 days of taking ephedrine regularly, or 90 days for that matter, cannot be higher than the level of ephedrine in plasma after taking ephedrine for 1-4 days. Moreover, as detailed above, studies of ephedrine have continued for as long as 50 weeks without serious adverse events being reported.¹⁵⁶ Accordingly, there is little or no evidence that duration of exposure to ephedrine alkaloid dietary supplements, when taken in recommended doses, is related to incidence of any serious adverse events.

In addition, the United States has extensive experience with ephedrine alkaloids and caffeine/ephedrine alkaloid combinations from OTC drug ephedrine alkaloid preparations and dietary intake of caffeine.¹⁵⁷ Americans have taken ephedrine alkaloids at a dosage of 25 mg every four hours, or 150 mg/day, in OTC asthma remedies for years.¹⁵⁸ When these remedies are taken with a cup of coffee, which can contain 100 mg of caffeine or more, the ephedrine alkaloid/caffeine intake exceeds the maximum ephedrine alkaloid/caffeine content in a single serving of Metabolife 356® (24 mg of ephedrine alkaloids/80 mg of caffeine). Accordingly, many Americans have been regularly consuming similar dosages of ephedrine in OTC preparations, alone, or in combination with caffeine, for many years without incident.

IV. Conclusion

As demonstrated above, Public Citizen failed to advance its position that dietary supplements containing ephedrine alkaloids present an "imminent hazard" to the public,¹⁵⁹ and failed to

¹⁵⁶ See, e.g., A. Astrup, et al., *The Effect and Safety of an Ephedrine/Caffeine Compound Compared to Ephedrine, Caffeine, and Placebo in Obese Subjects on an Energy Restricted Diet: A Double-Blind Trial*, 16 *Int'l Journal of Obesity* 269 (1992) (See Attachment A30); see also P.A. Daly, et al., *Ephedrine, Caffeine, and Aspirin: Safety and Efficacy for Treatment of Human Obesity*, 17 *Int'l Journal of Obesity* S73 (1993) (See Attachment A40).

¹⁵⁷ See, e.g., Patrick Summary at 1 (See Attachment A5); see also *Herb Information Greenpaper: Herbal Stimulants*, The Herb Research Foundation (citing the doses of caffeine generally contained in common food products) (See Attachment A41).

¹⁵⁸ See 51 Fed. Reg. at 35331.

¹⁵⁹ The evidence presented by Public Citizen is also insufficient to demonstrate that certain individuals or groups may be hypersensitive to ephedrine alkaloids and/or ephedrine alkaloid/caffeine combinations. As HHS noted in its denial of the aspartame citizen petition, "only well-controlled clinical trials which focus on specific endpoints would provide evidence of an effect in small populations of individuals." HHS Aspartame Petition Denial, at 5. (See Attachment A7).

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provide any new evidence relevant to the analysis. Public Citizen, like the petitioners involved in the aspartame and Feldene matters, relied upon anecdotal evidence that cannot establish a causal relationship between ephedrine alkaloids and the adverse events with which they are allegedly associated.¹⁶⁰

Public Citizen also failed to cite evidence counter to its position, contrary to an FDA regulation, even though it certified otherwise. Public Citizen failed to cite numerous well-controlled clinical trial abstracts and reports (e.g., the Cantox Report, the Harvard/ Columbia 6-Month Safety and Efficacy Trial, the 8-Week Columbia Study, and Dr. Astrup's studies, *inter alia*),¹⁶¹ and the pharmacological/ toxicological data on ephedrine alkaloids, all of which clearly establish that ephedrine alkaloids, consumed in dosages recommended by the industry (100 mg/day), are safe, with or without caffeine.

Each of the factors cited to support Public Citizen's petition may be easily refuted:

- **1,398 AERs As Evidence of Causation** - As FDA's website acknowledges, "there is no certainty that a reported adverse event can be attributed to a particular product."¹⁶² Accordingly, Public Citizen's reference to the 1,398 AERs collected by FDA over an eight year period cannot establish that ephedrine alkaloids present an "imminent hazard," particularly given that HHS refused to declare an "imminent hazard" after reviewing: (1) over 3,000 AERs collected over a two year period cited by CNI in support of its aspartame petition, and (2) over 2,800 AERs collected over a two year period cited by Public Citizen in its Feldene petition. Moreover, the number of AERs collected over an eight year period for dietary supplements containing ephedrine alkaloids is indeed significantly lower than the number of reports for products generally recognized to be safe and acceptable for the U.S. population - such as aspirin and acetaminophen. For example, in calendar year 2000, alone, the AAPCC determined that aspirin was plausibly related to at least 5,946 of the adverse events followed (including 52 deaths) and acetaminophen was plausibly related to at least 2,660 of the adverse events followed (including 99 deaths).¹⁶³

¹⁶⁰ See *id.* at 2; HHS Feldene Petition Denial, at 5 (See Attachment A11).

¹⁶¹ See Attachment A1.

¹⁶² See *The Special Nutritionals Adverse Event Monitoring System*, FDA CFSAN, Office of Special Nutritionals, <http://vm.cfsan.fda.gov/~dms/aems.html>.

¹⁶³ See Toby L. Litovitz, M.D., *2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System*, 19 *The American Journal of Emergency Medicine* 337 (Sept. 2001) (See Attachment A17); see *supra*, discussion at Section III(A)(1).

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- **The Haller/Benowitz and Woosley AER Analyses** - AER analyses, generally, are no more reliable for assessing causation than the AERs themselves because the AERs are not capable of proving causation and frequently lack medical records and other information necessary to rule out other causes of the events reported, such as concurrent drug use or underlying disease. Moreover, AER analyses are particularly subject to reviewer biases. Further, the results of the Haller/Benowitz analysis and the Woosley analysis differ widely from each other and the analyses performed by other experts on the same data set, and the Haller/Benowitz and Woosley analyses themselves have been widely discredited for flawed reasoning.
- **AAPCC Reporting Trends** - The fact that the rate of reporting to the AAPCC for events, allegedly associated with ephedrine alkaloids, increased from 1997 to 1999 has no bearing on the safety profile of ephedrine alkaloids. In fact, the increase in reporting is not unexpected, once the reporting rate is corrected for overreporting due to media attention and the fact that the sale of dietary supplements containing ephedrine alkaloids tripled during that time period.
- **AERs, Case Studies, and Anecdotal Evidence as Indicators of Risk** - The 1,398 AERs, case studies, and other forms of anecdotal evidence cited by Public Citizen cannot be used for risk assessment purposes. The types of adverse events reported in the AERs and case studies, allegedly associated with ephedrine alkaloids, are common events. For example, even under the "worst case scenario" the estimated number of serious adverse events, such as seizure, stroke, and heart attack, that occur in ephedrine alkaloid consumers is the same as, if not less than, the estimated number of such serious adverse events that occur in non-consumers.
- **Inapposite Comparisons to the Pharmacology/Toxicology of PPA, Amphetamine, and Methamphetamine** - Comparisons between synthetic ephedrine and PPA, amphetamine, and methamphetamine are scientifically irresponsible because the chemical structures, metabolism, tissue disposition, excretion, and/or potencies of synthetic ephedrine and the other substances differ.
- **Poorly Designed Studies** - The four so-called "studies" cited by Public Citizen (which actually include a case study and an animal study) are of poor design and fail to support, much less advance, Public Citizen's position that ephedrine alkaloids present an "imminent hazard" to the public.

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Accordingly, all five of the factors that HHS traditionally considers in determining whether an "imminent hazard" is present lead to the conclusion that dietary supplements that contain ephedrine alkaloids do not present an "imminent hazard".¹⁶⁴

- (1),(2) The severity and likelihood of harm to the public health that could occur during the completion of customary administrative proceedings.

There is no evidence that dietary supplements containing ephedrine alkaloids pose any hazard to health, much less an imminent one. To the contrary, as demonstrated by the Cantox Report, the studies summarized above, and the studies and reports listed in Attachment A1, the overwhelming weight of the evidence suggests that dietary supplements containing ephedrine alkaloids are safe and efficacious in supporting weight loss.

FDA has been evaluating the safety of dietary supplements that contain ephedrine alkaloids for eight years, and FDA's regulation of such products is currently on FDA's "B List" of regulatory priorities. Accordingly, if the agency were to conclude that such products now present an "imminent hazard," such a conclusion would be contrary to the administrative record, contrary to the GAO's conclusions, contrary to FDA's ongoing review of such products, and most importantly, contrary to the substantial scientific support for the safety of such products.

- (3) Possible harm from immediate suspension.

An immediate ban of dietary supplements containing ephedrine alkaloids would deprive millions of Americans of the only currently available product that is not only a safe, but an efficacious and inexpensive means of supporting weight loss.

- (4) Likelihood that, after the customary administrative process is completed, the product will be withdrawn from the general market;

Although FDA believes that certain restrictions on dietary supplements containing ephedrine alkaloids may be appropriate, the agency has never suggested that such products should be banned. Accordingly, after the

¹⁶⁴ See, e.g., HHS Penicillin Petition Denial, at 5 (See Attachment A10); HHS Feldene Petition Denial (See Attachment A11).

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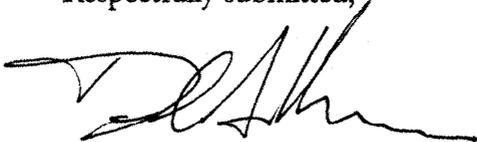
administrative process is completed, it is not at all likely that dietary supplements that contain ephedrine alkaloids would be withdrawn from the market.

(5) The availability of other approaches to protect the public health.

Although dietary supplements containing ephedrine alkaloids cannot and should not be banned, Metabolife strongly supports the promulgation of a reasonable, science-based regulation for ephedrine alkaloids, and looks forward to working with HHS and FDA toward that end. Such a regulation would include: (a) a limit of 25 mg of ephedrine alkaloids/serving, 100 mg of ephedrine alkaloids/day (commensurate with the science-based serving restrictions imposed by Hawaii, Michigan, Nebraska, Ohio, and Washington); (b) a prohibition on claims indicating that consumption of the product helps one to achieve an altered state of consciousness or euphoria, or provides a "legal" alternative for an illicit drug; (c) a detailed mandatory warning to ensure that only appropriate individuals use ephedrine alkaloid and ephedrine alkaloid/caffeine dietary supplement products; (d) a prohibition on sales to minors; (e) a prohibition on the use of synthetic ephedrine alkaloids in dietary supplements; and (f) no prohibition on ephedrine alkaloid/caffeine combinations.

For the foregoing reasons, we request that HHS deny Public Citizen's petition seeking an "imminent hazard" declaration regarding dietary supplements containing ephedrine alkaloids. We also request that HHS deny Public Citizen's request for issuance of a consumer advisory.

Respectfully submitted,



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VIA HAND DELIVERY

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Re: Dietary Supplements Containing Ephedrine Alkaloids – Docket No. 01P-0396

Dear Sir or Madam:

On behalf of our client, Metabolife International, Inc. (“Metabolife”), we hereby submit this response to the citizen petition filed by Public Citizen on September 5, 2001.

Please feel free to contact me if you have any questions or concerns.

Sincerely,



Paul D. Rubin

Enclosures

APPENDIX

1. Studies and Reports that Public Citizen Failed to Cite, Which Support the Safety Profile of Ephedrine Alkaloids.
2. Cantox Health Sciences International Report, *Safety Assessment and Determination of Tolerable Upper Limit for Ephedra*, Council for Responsible Nutrition, Dec. 19, 2000.
3. Grover M. Hutchins, *Letter to the Editor of the New England Journal of Medicine*, 344 N. Engl. J. Med. 1095-96 (2001); C.A. Haller and N.L. Benowitz, *Correspondence (Author's Reply)*, 344 N. Engl. J. Med. 1096 (2001).
4. The American Herbal Product Association ("AHPA"), Ephedra Trade Recommendation, (Feb. 10, 2000).
5. Report of Graham A. Patrick, Ph.D., R.Ph., dated Sept. 27, 2000; Graham A. Patrick, Ph.D., R.Ph., *Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids: Summary Conclusions*, Aug. 9, 2000; Graham A. Patrick, Ph.D., R.Ph., *Preliminary Commentary on Food and Drug Administration Proposed Rule on Limitations on Dietary Supplements Containing Ephedrine Alkaloids*, 1997.
6. General Accounting Office, *Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids* (July 1999).
7. Letter from the Department of Health and Human Services ("HHS") to James S. Turner, Swankin and Turner, Denying a Citizen Petition Seeking a Ban on Aspartame Based upon an "Imminent Hazard" Provision, Dated Nov. 21, 1986.
8. The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity 2001, HHS, www.surgeongeneral.gov/library.
9. George A. Bray, M.D., *Safety of Dietary Supplements Containing Ephedrine Alkaloids*, Aug. 8-9, 2000.
10. Letter from HHS to Karim Ahmed, Ph.D., Natural Resources Defense Council, Inc., Denying a Citizen Petition Seeking to Suspend the Approval of the Subtherapeutic Use of Penicillin and Tetracyclines in Animal Feeds Under an "Imminent Hazard" Provision, Dated Nov. 19, 1985.
11. Letter from HHS to Sidney M. Wolfe, M.D., Health Research Group, Denying a Citizen Petition Seeking to Ban the Use of Feldene (Piroxicam) in People Over Aged 60, Dated July 7, 1986.
12. Carol N. Boozer, et al., *Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Safety and Efficacy Trial* (Abstract), 9(1) Obesity Research 68 (2001) and 15(4) FASEB Journal A403 (2001).
13. Carol N. Boozer, et al., *An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-Blind Trial*, 25 Int'l Journal of Obesity 316 (2001).
14. De Jonge, et al., *Safety and Efficacy of an Herbal Dietary Supplement Containing Caffeine and Ephedra for Obesity Treatment*, 9(3) Journal of Obesity Research (Program Abstract PG20) (Oct. 7-10, 2001).

15. Belfie, et al., *Safety and Effectiveness of an Herbal Dietary Supplement Containing Ephedra (Ma Huang) and Caffeine (Guarana Extract) When Used in Combination With a Supervised Diet and Exercise Intervention*, 9(3) *Journal of Obesity Research (Program Abstract PG26)* (Oct. 7-10, 2001).
16. F.L. Greenway, *The Safety and Efficacy of Pharmaceutical and Herbal Caffeine and Ephedrine Use as a Weight Loss Agent*, 2 *Obesity Reviews* 199 (2001); Letter from Frank Greenway, M.D. to Paul D. Rubin, dated November 20, 2001.
17. Toby L. Litovitz, M.D., *2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System*, 19 *The American Journal of Emergency Medicine* 337 (Sept. 2001).
18. Tracy Wheeler & Jim Quinn, *Herbal Products Cause Ill Effects: Natural Remedies Can Prove Deadly*, *Akron Beacon Journal*, May 9, 2000.
19. Judith Jones, *Review of Cases Describing Events Associated with Exposure to Various Ephedrine Alkaloid-Containing Products*, Sept. 14, 2000.
20. C.A. Haller and N.L. Benowitz, *Adverse Cardiovascular and Central Nervous System Events Associated with Dietary Supplements Containing Ephedrine Alkaloids*, 343 *N. Engl. J. Med.* 1833-38 (2000).
21. Open Letter to the Public and the Scientific Community, a Response to a Paper on Ephedra by Haller and Benowitz Released in the *New England Journal of Medicine*, Ephedra Education Council Panel (Dec. 11, 2000).
22. Sorrel Schwartz, Ph.D., *Report Concerning Ephedrine in Herbal Preparations*, dated Sept. 27, 2000.
23. Letter to Dockets Management Branch, FDA, from Robert Stark, M.D., F.A.C.P., F.A.C.C., dated September 25, 2000; Letter from Robert M. Stark, M.D., F.A.C.P., F.A.C.C., to the Office on Women's Health, dated Aug. 8, 2000.
24. Ephedra Education Council: Facts on Ephedra, *Executive Summary of the HHS Ephedra Meeting*.
25. Arthur Andersen LLP, *Ephedra Survey Results: 1995-1999*, prepared for AHPA, dated Apr. 28, 2000.
26. Stephen Kimmel, *Summary of Incidence of Seizures, Strokes, and Myocardial Infarction in the Population and Estimations of Risk in the Population from Ephedra Products* (Selected Slides Used During the Kimmel Presentation at the Ephedra Hearing on Aug. 8-9, 2000).
27. Ephedra Education Council: The Facts on Ephedra, *An Examination of the Literature FDA Used in Evaluating the Physiological and Pharmacological Effects of Ephedrine Alkaloids*.
28. L. James, et al., *Sympathomimetic Drug Use in Adolescents Presenting to a Pediatric Emergency Department with Chest Pain*, 36 *Journal of Toxicology - Clinical Toxicology* 321 (1998).
29. Young, et al., *(-) Ephedrine and Caffeine Mutually Potentiate One and Another's Amphetamine-Like Stimulus Effect*, 61 *Pharmacology, Biochemistry, and Behavior* 169 (1998).
30. A. Astrup, et al., *The Effect and Safety of an Ephedrine/Caffeine Compound Compared to Ephedrine, Caffeine, and Placebo in Obese Subjects on an Energy Restricted Diet: A Double Blind Trial*, 16 *Int'l Journal of Obesity* 269 (1992).
31. S. Toubro, et al., *Safety and Efficacy of Long-Term Treatment with Ephedrine, Caffeine, and Ephedrine/Caffeine Mixture*, 17 (1 Supp.) *Int'l Journal of Obesity* S69 (1993).

32. W. Martin, et al., *Physiologic, Subjective, and Behavioral Effects of Amphetamine, Methamphetamine, Ephedrine, Phenmetrazine, and Methylphenidate in Man*, 12 *Clinical Pharmacology and Therapeutics*, 245-58 (1971).
33. L. Chait, *Factors Influencing the Reinforcing and Subjective Effects of Ephedrine in Humans*, 113 *Psychopharmacology* 381 (1994).
34. S. Toubro et al., *The Acute and Chronic Effects of Ephedrine/Caffeine Mixtures on Energy Expenditure and Glucose Metabolism In Humans*, 17 (3 Supp.) *Int'l Journal of Obesity and Related Metabolic Disorders* S73 (1993).
35. Arne Astrup, M.D., Ph.D., *Video Testimony for the USDHS Public Hearing Meeting: Safety of Dietary Supplements Containing Ephedrine Alkaloids*, Aug. 8-9, 2000.
36. *Health Journal: Ephedra Use Grows, But Some Question Its Safety for Dieters*, *The Wall Street Journal* (Apr. 6, 2001).
37. *Ephedra Makers Submit New Data to U.S. FDA*, *Reuters English News Service* (Dec. 20, 2000).
38. A. Astrup, et al., *Thermogenic Synergism Between Ephedrine and Caffeine in Healthy Volunteers: A Double-Blind, Placebo-Controlled Study*, 40(3) *Metabolism* 323 (1991).
39. A. Astrup, et al., *Thermogenic, Metabolic, and Cardiovascular Effects of a Sympathomimetic Agent, Ephedrine, a Double-Blind Placebo-Controlled Study*, 48 *Current Therapeutic Research* 1087 (Dec. 6, 1990).
40. P.A. Daly et al., *Ephedrine, Caffeine, and Aspirin: Safety and Efficacy for Treatment of Human Obesity*, 17 (1 Supp.) *Int'l Journal of Obesity* S73 (1993).
41. *Herb Information Greenpaper: Herbal Stimulants*, *The Herb Research Foundation*.