April 20, 2004

VIA UPS OVERNIGHT MAIL
Division of Dockets Management
FDA
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville MD 20852

Dear Dockets Management:

Please file the enclosed in Docket No. 1995N-0304.

Sincerely,

Jonathan W. Emord

Enclosures
April 20, 2004

VIA EMAIL dtroy@oc.fda.gov
AND UPS GROUND
Dan Troy
Chief Counsel
Food and Drug Administration
5600 Fishers Lane
Room 605, GCF-1
Rockville, MD

Re: Docket 95N-0304; Dietary Supplements Containing Ephedrine Alkaloids

Dear Dan:

I represent Nutraceutical Corporation. Before the final rule on the ephedra ban, “Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk,” 69 Fed.Reg. 6788 (February 11, 2004), the company sold a low dose whole-herb ephedra dietary supplement (containing less than 10 mg of ephedrine alkaloids per daily dose). The company filed comments in the rulemaking preceding the final rule, explaining that its product’s low levels of ephedrine alkaloids did not cause the harms which the final rule ultimately identified as the reason for the rule.

The attached scientific report from Dr. Glade confirms that there is no publicly available scientific evidence linking whole-herb ephedra with a daily dose level of ephedrine alkaloids lower than 10 mg with any of the cited harms. As you know, the rule does not preclude the sale of ephedra as a food (e.g., ephedra tea), which routinely includes higher per daily dose ephedrine alkaloid amounts without producing the cited harms. It would appear that under 21 U.S.C. § 342(f)(1)(A) FDA must demonstrate the presence of risks of harm at every dose level to justify a total ban. Yet, FDA has no substantive dose-dependent analysis in the final rule. Nutraceutical Corporation sought just such an exception in its April 7, 2003 and January 30, 2004 Comments.
I am supplying Dr. Glade’s scientific report (attached) to afford you the opportunity to reconsider the prudence of a total ban and am simultaneously placing this letter and the report in the official docket of the proceeding.

Sincerely,

[Signature]
Jonathan W. Emord

Attachments
A Review of the Safety of the Consumption of Ephedrine Alkaloids

Based on my review of the reliable and credible published peer-reviewed scientific literature regarding the effects of the consumption of ephedrine alkaloids, with particular reference to ephedrine, I find the following conclusions supported by the evidence:

1. Ephedrine alkaloids, including ephedrine from any source, have activity in humans similar to sympathomimetic compounds, with potency that is dependent on their concentration in the plasma.
2. The daily consumption of 20 mg or more of ephedrine alkaloids may be associated under some circumstances with acute or cumulative adverse effects on the cardiovascular system in susceptible individuals; however, the daily consumption of 20 mg or more of ephedrine alkaloids also has been shown to have no acute or cumulative adverse effects on the cardiovascular system in all but a few susceptible individuals.
3. The daily consumption of 10 mg or less of ephedrine alkaloids is not associated with acute or cumulative adverse effects on the cardiovascular system.

Ephedra, Ephedrine and the Ephedrine Alkaloids

The ephedrine alkaloids L-ephedrine, D-pseudoephedrine, L-norephedrine (phenylpropanolamine), L-N-methylephedrine, D-norpseudoephedrine, D-N-methylpseudoephedrine, and other minor related alkaloids are members of a large family of structurally related pharmacological compounds that are called sympathomimetics because they mimic the effects of the neurotransmitters, epinephrine and norepinephrine, by binding to alpha- and beta-adrenergic receptors throughout the body, including the cardiovascular system.1-4

In addition to their direct pharmacological effects, many (but not all) of these compounds also stimulate the release of norepinephrine from nerve endings, further increasing the transient sympathomimetic effects of those compounds that do stimulate the release of norepinephrine.1 Although varying widely in their potency, in susceptible individuals some sympathomimetic compounds in sufficient amounts may induce cardiac arrhythmias in individuals with underlying coronary artery disease; any individual arrhythmic event may be fatal.1,5,6 Furthermore, artificial sympathomimetic drugs, such as beta-agonists (for example, albuterol) and xamoterol, as well as phosphodiesterase inhibitors that potentiate the effects of beta-agonists (for example, milrinone and enoximone), may increase mortality in patients with congestive heart failure.1,7-9

By analogy with the general pharmacology of the class of all sympathomimetic compounds, it has been suggested that dietary supplements containing ephedrine alkaloids may induce short-term and long-term increases in the risks of sudden stroke, heart attack or death or of exacerbations in the severity of congestive heart failure or underlying coronary artery disease in susceptible individuals in whom the ephedra alkaloids may produce sustained increases in blood pressure.1,10,11
Clinical Trials Providing Data concerning the Safety of the Ephedrine Alkaloids

Although the proportions of the various ephedrine alkaloids in botanical species vary from one species to another, in most species used commercially (i.e., plants such as *Ephedra sinica* Stapf, *Ephedra equisetina* Bunge, *Ephedra intermedia* var. *tibetica* Stapf, *Ephedra distachya* L., *Sida cordifolia* L. and *Pinellia ternata* (Thunb.) Makino), ephedrine typically is the predominant ephedrine alkaloid present in raw botanicals and in extracts produced from such botanicals. Consequently, studies of the effects and actions of the ephedrine alkaloids have focused on the effects and actions of ephedrine, either as a component of a botanical extract or as a synthetic dietary supplement ingredient.

Acute Effects of Initial Exposure to Ephedrine

Apparently healthy individuals with systolic and diastolic blood pressures within the broad ranges of “normal” for these characteristics and naïve to the ephedrine alkaloids have consumed amounts of ephedrine ranging from 10 mg to 60 mg in studies of the acute post-consumption effects of this compound. Effects on systolic and diastolic blood pressure have not been observed consistently. For example, while the acute consumption of 60 mg of ephedrine was reported to produce an increase in the mean average diastolic blood pressure measured every 10 minutes for 4 hours post-consumption in one study, diastolic blood pressure at 90 minutes post-consumption was reportedly not affected by the consumption of 50 mg to 70 mg of ephedrine in another study, although systolic blood pressure was increased significantly by an average of 13 mm Hg at 90 minutes post-consumption. In other studies, systolic blood pressure increased by between 6 mm Hg and 20 mm Hg and mean heart rates also were increased during the 8 hours following the consumption of 50 mg of ephedrine. However, in only one study was diastolic blood pressure affected following the consumption of 50 mg of ephedrine, increasing for 3 hours post-consumption.

Although effects on systolic blood pressure and heart rate have been reported following the consumption of smaller amounts of ephedrine, those amounts have not affected acute post-consumption diastolic blood pressures. Nonetheless, the consumption of 40 mg of ephedrine produced increases in systolic blood pressure (mean increase: 5 mm Hg) and in heart rate (mean increase: 7 bpm) at an undisclosed time during the 8 hours following consumption. Similarly, the consumption of 30 mg of ephedrine produced subsequent significant increases in systolic blood pressure and heart rate during 4 to 8 hours post-consumption.

The consumption of 25 mg of ephedrine has been followed by increases in mean heart rate and mean systolic blood pressure when measured at 2.5 and 5 hours post-consumption in healthy normotensive individuals. Although the elevation in heart rate...
remained at 7.5 hours post-consumption, mean systolic blood pressure had returned to its
pre-consumption level by 7.5 hours post-consumption. In contrast, the consumption of
25 mg of ephedrine has not been followed by changes in systolic or diastolic blood
pressures or heart rates when measured one hour post-consumption in normotensive
adults with and without airway disease or 0.5, 1, 2, 3, 4, 5, 6 and 7 hours post-
consumption in normotensive adults with and without asthma.

The consumption of 20 mg of ephedrine has induced both no responses in healthy
normotensive individuals and some responses in others, according to four studies. In one study, the consumption of 20 mg of ephedrine had no effects on systolic blood
pressure, diastolic blood pressure or heart rate. In another, although heart rate was not
affected 60 minutes post-consumption, mean arterial blood pressure was increased by an
average of 23 mm Hg, a larger increase than those reported to follow the consumption of
2 to 3 times as much ephedrine (and therefore possibly artefactual or reflective of poor
subject selection). In contrast, other investigators reported that 3 hours after the
consumption of 20 mg of ephedrine, heart rate was increased by an average of 4 bpm
while systolic and diastolic blood pressures were not different from pre-consumption
levels. In a study in which investigators confirmed the consumption of 19.4 mg of
ephedrine as a component of a powdered preparation of Ma Huang herb, some subjects at
both 3 and 12 hours post-consumption experienced increases in systolic blood pressure or
heart rate, some experienced increases in both; some experienced notable decreases in
blood pressure or heart rate; some experienced decreases in both; and some subjects
experienced no changes in these measurements.

Subjects experienced no acute effects on systolic or diastolic blood pressures measured
every half-hour for 3 hours following the consumption of 10 mg of ephedrine. However, heart rate was increased by an average of 1.5 bpm at 3 hours post-
consumption.

The acute effects of ephedrine also have been studied in healthy individuals without
hypertensive disease who received 5 mg or 10 mg of ephedrine via intranasal delivery. Cardiovascular variables (systolic blood pressure, diastolic blood pressure, heart rate)
measured pre-administration and after 0.5, 1, 2, 3, 4, 6 and 8 hours remained unaffected
by the intranasal administration of 5 mg of ephedrine while 10 mg produced small
significant increases in only systolic blood pressure and heart rate that persisted for only
4 hours.

For comparison purposes, this study also examined the acute effect of oral consumption
of 50 mg of ephedrine. All 3 methods of supplementation (5 mg intranasally, 10 mg
intranasally, 50 mg orally) were observed to increase the plasma concentrations of
ephedrine. The time to achieve maximum plasma ephedrine concentration and the
plasma half-life were not significantly different. The maximum plasma concentration
that was achieved following the administration of 5 mg intranasally was about 10% of
that achieved following the consumption of 50 mg of ephedrine (13.0 ng/mL and 137.8
ng/mL, respectively). The maximum plasma concentration that was achieved following
the administration of 10 mg intranasally was about 20% of that achieved following the consumption of 50 mg of ephedrine (28.3 ng/mL and 137.8 ng/mL, respectively). These data suggest that the mode of administration had little effect, if any, on the pharmacokinetics of ephedrine and that 5 mg and 10 mg administered intranasally were bioequivalent to 5 mg and 10 mg consumed orally.

Interestingly, when the data obtained in the 4 studies that have examined the pharmacokinetics of ephedrine are combined, with oral intakes ranging from 19.4 mg to 50 mg, the maximum plasma concentration of ephedrine achieved post-consumption appears highly correlated with the amount of ephedrine consumed ($r = 0.9591; p<0.01$). Furthermore, when the data obtained following intranasal administration of 5 mg or 10 mg is added, this tight correlation is maintained ($r = 0.9576; p<0.001$). Although this correlation analysis is not definitive because it is diminished by examining only mean maximum plasma ephedrine concentrations (the only data available) rather than the individual maximum plasma ephedrine concentrations measured in each subject, the results remain consistent with the conclusion that 5 mg and 10 mg of ephedrine administered intranasally behave as if they were administered orally. This conclusion is strengthened by the observation that the plasma half-life of ephedrine following intranasal administration of 5 mg (6.0 hours) or 10 mg (6.0 hours) is not different from the average plasma half-life of ephedrine estimated in the studies of ephedrine consumption (5.8 hours). In addition, the time to achieve maximum plasma ephedrine concentration was similar regardless of mode of supplementation (average median time to achieve maximum plasma ephedrine concentration: 2.6 hours). Consequently, it may be predicted that the consumption of 5 mg of ephedrine will be expected to be similar to that of the intranasal administration of 5 mg of ephedrine and will be expected to be without effect on the cardiovascular system.

Effects of Chronic Exposure to Ephedrine

Chronic consumption of ephedrine as the sole dietary supplement ingredient has consistently been without effect on blood pressure. Daily consumption of 60 mg of ephedrine (20 mg t.i.d.) had no effect on single measurements of systolic or diastolic blood pressures obtained at irregular lengths of time after the most recent consumption of ephedrine following 4, 8, 12, 16, 20 or 24 weeks of dietary supplementation in a placebo-controlled trial. In contrast, 4 weeks of daily dietary supplementation was reportedly associated with increased mean heart rates; the significant increase in heart rate of 5 to 8 bpm persisted through 24 weeks of supplementation. In addition, 44% of the subjects consuming 60 mg of ephedrine daily experienced side effects, compared to 24% of the subjects consuming placebo. Some of the subjects who withdrew from consumption of ephedrine experienced “rebound symptoms” (headache and fatigue following discontinuation of ephedrine supplementation).

Daily consumption of 75 mg (25 mg t.i.d.) or 150 mg (50 mg t.i.d.) of ephedrine for 1, 2 or 3 months had no effect on single measurements of systolic or diastolic blood pressures in obese men and women consuming restricted low calorie diets in a placebo-controlled clinical trial. However, although daily consumption of 75 mg had no effect on heart
rate, daily consumption of 150 mg of ephedrine elevated heart rates (by about 8 bpm) at measurements obtained after 1, 2 and 3 months of supplementation. There was no difference in the incidence of side effects among subjects consuming 75 mg of ephedrine or placebo; however, the incidence of side effects was significantly greater among the subjects consuming 150 mg of ephedrine daily. In contrast, in another study, no side effects were observed during 2 weeks of daily dietary supplementation with either placebo or 150 mg of ephedrine (50 mg t.i.d.).32

The conclusions of these reports30-32 have been criticized with the argument that single measurements of blood pressures are insufficiently sensitive to identify transient increases of blood pressure that may occur subsequent to the consumption of ephedrine alkaloids, as was found to occur in one study that employed continuous ambulatory blood pressure monitoring of subjects consuming ephedrine and caffeine in combination.1,33 Although that possibility cannot be definitively excluded, the blood pressure measurements in these 4 trials were obtained during the time period (that is, between one and 6 hours post-consumption) when plasma ephedrine concentration was either near-maximal (plasma ephedrine concentration one hour after the consumption of ephedrine has been reported to be near 95% of maximum concentrations28), maximal, or greater than one-half maximal.18,27-29

In studies of the acute effects of single exposures to 5 mg or 10 mg of ephedrine, cardiovascular variables (systolic blood pressure, diastolic blood pressure, heart rate) measured pre-administration and after 0.5, 1, 2, 3, 4, 6 and 8 hours remained unaffected by the intranasal administration of 5 mg of ephedrine, while single exposure to 10 mg produced small significant increases in only systolic blood pressure and heart rate that persisted for only 4 hours.18,19,26 Although the safety of chronic exposure to 5 mg or 10 mg of ephedrine or total ephedrine alkaloids has not been studied, the measurements taken during the 8 hours following single acute exposures to these amounts of ephedrine suggest that no carry-over effect would occur from exposure to exposure and therefore that no adverse cardiovascular effect would become manifest during cumulative daily exposures to these amounts of ephedrine or total ephedrine alkaloids.

Several investigations of the safety of dietary supplements containing ephedrine alkaloids have considered all consumption of such compounds, even when combined with other potentially sympathomimetic substances. The findings of these investigations support the conclusion that very few if any adverse reactions are associated with the daily consumption of 20 mg or less of ephedrine alkaloids. For example, the influence of chronic dietary supplementation with ephedrine alkaloid-containing ingredients (alone or in combination with other substances) on the occurrence of the specific adverse reaction, hemorrhagic stroke, was examined in the Hemorrhagic Stroke Project.34 In this retrospective case-control study, the odds ratios (OR) for hemorrhagic stroke were calculated after adjustment for race, history of hypertension, current cigarette smoking, education, primary family history of hemorrhagic stroke and alcohol consumption. The adjusted OR for hemorrhagic stroke among individuals who had consumed any amount of ephedrine alkaloids during the 3 days immediately prior to data collection was 1.00
(95% confidence interval (CI): 0.32, 3.11), indicating that the risk among these individuals was the same as that among individuals who had not consumed any ephedrine alkaloid-containing ingredients during the immediately preceding 3 days. The adjusted OR for hemorrhagic stroke among individuals who had consumed any amount of ephedrine alkaloids during the 3 days immediately prior to data collection was not affected by the amount of ephedrine alkaloids consumed during this time (OR, less than 33 mg daily: 0.13; 95% CI: 0.01, 1.54; OR, 33 or more mg daily: 3.59; 95% CI: 0.70, 18.35). Similarly, the adjusted OR for hemorrhagic stroke among individuals who were consuming any amount of ephedrine alkaloids regularly at the time of data collection was not increased (OR: 1.11 (95% CI: 0.34, 3.56)), and the adjusted OR for hemorrhagic stroke among individuals who were consuming any amount of ephedrine alkaloids regularly at the time of data collection was not affected by the amount of ephedrine alkaloids being consumed (OR, less than 33 mg daily: 0.13; 95% CI: 0.01, 1.57; OR, 33 or more mg daily: 5.89; 95% CI: 0.84, 41.33).

In a meta-analysis of randomized placebo-controlled clinical trials in which some subjects consumed ephedrine alkaloids (alone or in combination with other substances), it was reported that when all ephedrine intakes were combined, the chronic consumption of greater than 40 mg ephedrine alkaloids was reported to be associated with significantly increased risks for psychiatric symptoms, autonomic hyperactivity, heart palpitations and upper gastrointestinal tract distress, while the risks for hypertension and headache were not increased.35-37 The investigators were unable to distinguish the risks associated specifically with the chronic daily consumption of 10 mg to 20 mg of ephedrine alkaloids because insufficient numbers of adverse reactions were associated with these low levels of intake, compared to the numbers of adverse reactions that were associated with daily intakes of 40 mg or more.

A review of adverse reaction reports that was published in 2000 reported that 10 of 11 adverse events that could "definitely" or "probably" be attributed to the consumption of ephedrine alkaloids were associated with consumption of more than 20 mg daily for more than one month.38 In addition, 10 of 15 adverse events that "possibly" were related to the consumption of ephedrine alkaloids were associated with chronic consumption of more than 20 mg daily. Three others were related to daily consumption of 20 mg for more than one year and the other 2 were related to the daily consumption of 12 mg for more than one month.

Conclusions

The data reviewed above support the following conclusions:

1. Ephedrine alkaloids, including ephedrine from any source, have activity in humans similar to sympathomimetic compounds, with potency that is dependent on their concentration in the plasma.

2. The daily consumption of 20 mg or more of ephedrine alkaloids may be associated under some circumstances with acute or cumulative adverse effects on
the cardiovascular system in susceptible individuals; however, the daily consumption of 20 mg or more of ephedrine alkaloids also has been shown to have no acute or cumulative adverse effects on the cardiovascular system in all but a few susceptible individuals.

3. The daily consumption of 10 mg or less of ephedrine alkaloids is not associated with acute or cumulative adverse effects on the cardiovascular system.
To avoid publication of his signature on the public docket, Dr. Glade has placed his original signature on file at Emord & Associates, P.C.
Literature Cited


