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Comment to the FDA regarding Docket: 95N-0304-Dietary Supplements Containing Ephedrine Alkaloids

We thank the FDA for the opportunity to provide public comment regarding **Docket: 95N-0304- Dietary Supplements Containing Ephedrine Alkaloids.**

I am a Professor of Preventive Medicine and Public Health at the University of Kansas School of Medicine in Wichita, Kansas and Director of the University of Kansas Master of Public Health Program at the same institution. I also am the Associate Dean for Research at the School of Medicine. A majority of my work includes research and teaching activities in the fields of chronic disease epidemiology, environmental epidemiology, and health promotion. I am an epidemiologist, and my specialty is in the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations. I conduct extensive research on various topics in chronic disease epidemiology, environmental epidemiology, and health promotion. I publish the results of my research in peer-reviewed scientific journals. I teach a variety

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of courses in epidemiology and public health at the University of Kansas, including neuroepidemiology.

My experience, training, and research expertise qualifies me to make comment on the Docket 95N-0304- Dietary Supplements Containing Ephedrine Alkaloids.

General Comment

Epidemiology concerns itself with identifying a causal association between external factors, such as exposure to a chemical or compound, and a disease or diseases. Epidemiology generally is the best evidence available to scientists interested in determining whether a disease is causally related to use of or exposure to a substance.

Controlled epidemiological studies are employed by scientists to determine whether the rate of disease in a population (such as the population of people who use ephedra alkaloids) represents the background rate of occurrence of the disease or is a result of the exposure to the substance (ephedra alkaloids).

Epidemiologists and other scientists value the importance of properly designed, controlled and conducted studies. A proper study design must precisely define the hypothesis to be tested and the background rate of the disease at issue. Only through a properly designed study can scientists answer the question whether the rate of occurrence in an exposed population is greater than the rate of occurrence in the unexposed population. Once it is determined that the rate of occurrence of a disease is greater in an exposed population, we say there is an association between the exposure and the disease. However, an association does not establish that the exposure caused

the disease. See Table 1 for levels of evidence and grading of recommendations by study design published by the American Heart Association (Goldstein, et al 2002).

Table 1. Levels of Evidence and Grading of Recommendations (American Heart Association 2002)

Level of evidence

Level I	Data from randomized trials with low false-positive and low false-negative errors
Level II	Data from randomized trials with high false-positive or high false-negative errors
Level III	Data from nonrandomized concurrent cohort studies
Level IV	Data from nonrandomized cohort studies using historical controls
Level V	Data from anecdotal case series

Strength of recommendation

Grade A	Supported by Level I evidence
Grade B	Supported by Level II evidence
Grade C	Supported by Level III, IV, or V evidence

There can be a distortion of an association between exposure and disease due to the simultaneous presence of another factor or factors. Before medical science recognizes a causal relationship, science must consider temporal relationships, alternative explanations, confounding exposures, confounding diseases, cessation of exposure, strength of the association, dose-response relationship, and biological plausibility.

An example of a confounding factor is instructive in understanding the difference between an association and a direct causal nexus. Patients who are on antihypertensive (high blood pressure) medications may have an increased risk of stroke over the general population. However, it does not necessarily follow that the

antihypertensive medication causes strokes. Rather, it may be that persons who are hypertensive are at a greater risk of stroke than the general population.

When the rate of occurrence of a disease is greater in an exposed population than in an unexposed population, we say there is a positive association. When the rate of occurrence of a disease in an exposed population is less than in an unexposed population, we say there is a negative association.

There is a generally accepted methodology for determining whether exposure to a chemical substance, such as ephedrine or ephedra alkaloids, causes an adverse effect, such as stroke, seizures, or myocardial infarction. That methodology begins with the formulation of a hypothesis (do ephedra alkaloids cause such events), which then must be tested by way of well-designed and carefully controlled epidemiological studies.

Controlled epidemiology may be accomplished by way of different study designs, and if well designed, can demonstrate whether there is a statistically significant association between the exposure (ephedrine or ephedra alkaloids) and the disease condition (stroke, seizures, myocardial infarction). Unless the association observed has statistical significance, a valid association has not been established.

If a statistically significant association is demonstrated in controlled epidemiological studies, the next step is to determine whether the association is causal or merely coincidental.

For example, a high percentage of individuals suffering from obesity may decide to use ephedrine or ephedra alkaloids for weight management, and it is well established that obese individuals (independent of ephedrine or ephedra alkaloids intake) are at high risk for a number of diseases, including heart attacks and stroke.

Therefore, if a study is performed to determine whether ephedrine users have a higher incidence of heart attacks and strokes than the general population, the answer could be yes (because many of the ephedrine users are obese), but this would not establish that ephedrine or ephedra alkaloids cause heart attacks or strokes. Rather, it would signify what is already known that obese individuals have a high incidence of heart attacks and strokes, regardless of whether they do or do not use ephedrine.

Thus, many factors must be considered before medical science will recognize that a causal relationship exists.

Those factors include examining the strength of the association, whether association has been demonstrated in other well designed controlled studies, the effect of dose on onset and progression of the disease, the temporal relationship between the exposure and onset of the disease, the latency between exposure and disease onset, the mechanism by which the drug acts upon biological systems, whether a causal relationship is biologically plausible, and whether other more likely causes can be eliminated. Once tested, the results should be published in a peer-reviewed scientific journal, and the results should be confirmed through subsequent testing of the sample hypothesis.

In medical science, as in other sciences, one cannot confirm opinions about causal relationships without appropriate testing. An opinion that there is a causal relationship between a particular chemical agent and a disease will not be recognized as valid unless it is supported by such testing.

Further, in the absence of testing data, the scientist or physician cannot conclude that a causal relationship exists, even if no other explanation is apparent.

Despite the extensive use of ephedra alkaloids in the United States, with hundreds of millions of caplets sold annually, we note no controlled epidemiologic studies that support an association between ingestion of ephedra alkaloids, whether ingested alone or with caffeine, and stroke, seizure, or myocardial infarction. We know of no evidence, with hundreds of millions of caplets sold annually, of increases in the rates of those diseases in the U.S. population. In fact, those rates are either stable or declining. No "spike" exists in the rates to our knowledge.

In the absence of population-based epidemiological evidence, one must be careful not to conclude that stroke, seizure, or myocardial infarction in an individual exposed to ephedra alkaloids was caused by ephedra alkaloids, either alone or in combination with caffeine.

In the absence of epidemiologic studies, the next best evidence available to the scientific community are controlled clinical trials in humans that evaluate the safety and efficacy of a product. Controlled clinical studies are designed to satisfy the scientific method. They begin with a hypothesis, and they seek to prove or disprove the hypothesis.

The body of scientific literature supporting the safety and efficacy of ephedra alkaloids and the substantial other evidence supporting the safety of ephedra alkaloids is important because general acceptance of scientific principles arises from both the quality and the quantity of such evidence. Controlled clinical trials are better quality than anecdotal reports, for example, and multiple studies tend to confirm the accuracy of the results.

The controlled clinical trials with ephedrine involve hundreds of subjects. Yet, none of the studies has reported significant adverse events. More importantly, none of the studies has included a single subject who experienced stroke, seizure, or myocardial infarction while consuming ephedra alkaloids, despite treatments for as long as twelve months. Clinical trials such as those of Boozer (2001 and 2002) and Astrup (1986, 1990, 1991, 1992, 1995) are scientifically sound.

Generally accepted scientific methodologies for evaluating whether there exists a possible association between a substance, such as ephedra alkaloids, alone or in combination with caffeine, and an injury, do not permit scientists to ignore the results of controlled clinical trials that do not reveal any occurrence of the suspect disease and, instead, to rely solely upon anecdotal reports, animal studies, and information regarding structurally-related compounds. Indeed, conclusions based upon such limited materials are inherently unreliable.

One might hypothesize that, because one chemical compound causes a disease, another chemical compound might cause the same disease. However, unless confirmed in appropriately controlled scientific studies, the hypothesis never rises above a theoretical possibility.

Similarly, while anecdotal adverse event reports may give rise to a hypothesis that must be tested, they cannot be used to quantify any possible risk or to determine who in a population may be at risk. Individual adverse events cannot be assumed to be associated with or caused by an exposure. That principle applies whether a case report is reported individually or whether it is plucked out of larger group case reports. This was repeatedly pointed out in the recent Rand Report, commissioned by NIH.

Generally, case reports and anecdotal adverse event reports reflect only reported data and not scientific methodology. Often there is little or no patient history, treatment history, or a description of confounding factors that might discount a true association. Accordingly, they cannot be relied upon to establish a causal relationship and doing so are inconsistent with accepted scientific methodologies. Even those case reports that attempt to rule out other causes cannot account for those events that are idiopathic or idiosyncratic and would have occurred in the absence of the exposure. Again, conclusions about causation, when derived from case reports and adverse event reports, are unreliable.

Animal and laboratory testing also may be informative on some issues, but in and of themselves, they cannot answer the human causation question. It is particularly inappropriate to rely upon animal studies to prove causation when the animals in the study did not even experience the disease at issue. In other words, one cannot demonstrate that, when exposed to a compound, an animal experienced effect A and thereby conclude that a human will experience effect B when exposed to the same compound. Conclusions about human causation derived from animal studies must be made with caution.

The Rand Report of 2003

The National Institutes of Health commissioned the Rand Corporation to examine the public health issues surrounding the use of ephedra containing products ("Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects"). I have reviewed the Rand Corporation report and wish to make the following statements regarding its content, as it relates to my comment on Docket: 95N-0304- Dietary Supplements Containing Ephedrine Alkaloids.

1) Using a pooled analysis (meta-analysis) of clinical trials where ephedra or ephedrine was used for weight loss, the investigators excluded over half (26 of 46 trials) for various reasons. Of the remaining 20 trials, only five tested herbal ephedra-containing products. Nevertheless, the investigators found a statistically significant increase in short-term weight loss compared to placebo.

2) The investigators claim that "No studies have assessed the long-term effects of ephedra-containing dietary supplements or ephedrine on weight loss; the longest duration of treatment in a published study was six months." This is not accurate. Proceedings of the 2002 International Congress on Obesity reported a controlled clinical trial by Filozof et al ("The Effect of Ephedrine Plus Caffeine After a 4-week Portion Controlled Diet"), which showed mean weight and waist-loss in the ephedrine/caffeine group that was significantly higher compared to the placebo group for up to one year of treatment.

3) In terms of efficacy for physical performance enhancement, the Rand report noted the effect of ephedrine on athletic performance was evaluated in seven studies. Ephedra had not been evaluated for physical performance enhancement. It was felt these studies did not generalize to the entire population because of lack of sample size. However, the data were noted to " support a modest effect of ephedrine plus caffeine on very short-term athletic performance".

4) In terms of safety issues, it was noted that clinical trials are often too small to "adequately assess the possibility of rare outcomes...Even in aggregate, the clinical trials enrolled only enough patients to detect a serious adverse event rate of at least 1.0 per 1,000." However, we know from the 2003 Heart and Stroke Statistical Update that the background rate of age-adjusted stroke incidence rates (per 1,000 person-years) are 1.78 for white men, 4.44 for black men, 1.24 for white women and 3.10 for black women. For all four of these groups the combined trials would be large enough to detect the normal rate of stroke in the population, plus any additional potential risk from the dietary supplement if it existed. If the trials had focused on males only, the background rate for blacks and whites is 6.22 per thousand, and the (combined) trials are large enough to detect the background rate for stroke. For females, the combined rate is 3.34 per 1000, and the same conclusion can be drawn.

Similarly, based on the National Institute of Heart Lung and Blood Diseases Framingham Heart Study in its 44 year follow-up of participants and 20 year follow-up of their offspring, the average annual rates of first major cardiovascular events rise from 7 per 1000 men at ages 35-44 to 68 per 1000 at ages 85-94. For women, comparable

events appear 10 years later in life (Heart and Stroke 2003). The clinical trials are large enough to detect such events.

In the United States, new seizure disorders are diagnosed at a rate of 20-60 per 100,000 per year (Hauser, 1993). With more than 12 million ephedra users, between 2,400 and 7,200 seizures would be expected. If there was a causal link between use of ephedra-containing products and seizures, thousands and thousands of ephedra-related seizures should have been reported.

5) For rare events, the correct research design in epidemiology for decades has been the retrospective case-control study. In fact the case-control design was specifically a solution to the study of rare, chronic diseases (rare events). This fact can be found in numerous epidemiological textbooks at both the introductory and advanced level. Indeed, the summary of the Rand report specifically notes, "Continued analysis of case reports cannot substitute for a properly designed study to assess causality. A case control study would probably be the study design of choice" This is correct. However, multiple retrospective case control studies need to be carried out to assess realities of the public health impact of ephedra. This could be done, as case control designs are quick and relatively inexpensive, and the exposure at the population level is relatively high - 1% of a multistate survey reported use of ephedra products ("Use of Nonprescription Weight Loss Products") published in the Journal of the American Medical Association in 2001. This was based on 1996-1998 data. It would be a higher percentage in 2003.

6) Such a case-control has been done by Yale University, and recently published in Neurology ("Use of Ephedra-containing Products and Risk for Hemorrhagic Stroke" by Morgenstern et al). The abstract follows below.

> **ABSTRACT**: This case-control study examined the associations between Ephedra use and the risk for hemorrhagic stroke. For use of *Ephedra* at any dose during the 3 days before the stroke, the adjusted OR was 1.00 (95% CI to 0.32 to 3.11). For daily doses of $\leq$ 32 mg/day, the OR was 0.13 (95% CI 0.01 to 1.54), and for > 32 mg/day, the OR was 3.59 (95% CI 0.70 to 18.35). *Ephedra* is not associated with increased risk for hemorrhagic stroke, except possibly at higher doses.
> *NEUROLOGY* 2003;60:132-135

This study did not find statistically significant associations between ephedra consumption and hemorrhagic stroke at any dosage level. Claims to the contrary in the FDA News are incorrect, and demonstrate misunderstanding of what a 95% confidence interval means. A confidence interval (CI) is "the computed interval with given probability, e.g., 95%, that the true value of a variable such as a mean, proportion, or rate is contained within the interval (Last, Dictionary of Epidemiology, 2001). At the highest dosage level (> 32 mg/day) the bottom of the 95% confidence interval was 0.70. For this to be a statistically significant association it would need to be greater that 1.0. Therefore, there are no statistically significant associations of any kind in this epidemiologic study of ephedra and hemorrhagic stroke.

Nevertheless, it is encouraging that case control studies are now beginning to appear in the literature. More epidemiologic case control studies are needed.

7) The Rand report used a system of "sentinel events" and "possible sentinel events" to classify case reports. Part of the material they reviewed was from the

Metabolife consumer calls system. I have reviewed all of these consumer calls as a consultant for Metabolife. They are, as noted in the Rand report itself, of very poor quality. I do not see how they could be rationally used in a sentinel events analysis. Even the Rand report notes, "For rare outcomes, we reviewed case reports, but a causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven....Classification of a sentinel event does not imply a proven cause and effect relationship."

8) Finally, the authors of the Rand report should be commended for noting the "numerous gaps in the literature regarding the efficacy and safety of ephedra-containing dietary supplements". Hypothesis testing studies are very much needed to fill these gaps so that our policy around ephedra products can be scientifically based.

Based on the population-based epidemiology carried out to date, I do not believe that dietary supplements containing ephedrine alkaloids present a significant or unreasonable risk of illness or injury under conditions of recommended use as suggested in labeling, or if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.

The readers should note that I received compensation from Metabolife Inc. for the time involved in writing this comment, however the opinions expressed herein are my own.

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