



*Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care*

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

Comments on the Safety Evaluation of Ephedra

by

R. William Soller, Ph.D.

Senior Vice President and

Director of Science & Technology

Consumer Healthcare Products Association

at the

Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids

The Department of Health and Human Services' Office on Women's Health,

United States Public Health Service

August 8-9, 2000

The Consumer Healthcare Products Association (CHPA) is a 119-year-old trade organization representing the producers of quality dietary supplements and nonprescription medicines. CHPA has over 200 member companies across the manufacturing, distribution, research, marketing and supply sectors of the self-care industry. The issue of ephedra safety, as raised by this meeting, affects CHPA members who market ephedra-containing dietary supplement products as well as other members who market certain over-the-counter (OTC) nasal decongestant and weight control products.

By introduction, the core issues surrounding a consideration of ephedra's safety relate to the use of adverse experience reports (AERs) as a foundation for public health decisions about product availability and labeling. CHPA manufacturers take very seriously any individual report about their products' safety, and we certainly feel compassion for those that believe they have suffered from use of dietary supplements or OTC medicines.

As scientists, however, we have the obligation to view data objectively and often in the abstract, so as to come to a deliberative decision about the quality and strength of the underlying data that might be the basis for public health decisions about ingredient safety. Fortunately, there is an accepted process on how to undertake such scientific/regulatory decisions.

Scientific/regulatory decisions on ingredient safety are made case-by-case, in a weight-of-all-the-evidence, data-driven and dialogue-driven process that includes all the relevant data and information. Such public health decisions that may affect ingredient availability or labeling must be based on data that are scientifically documented, clinically significant and important to the safe and effective use of the product by the consumer. This is a logical, long-standing FDA policy on consumer product issues (e.g., *Fed. Reg.* 47:54754,

1982), that ensures all the evidence is brought to bear on the issue and that the ultimate public health decision is based on scientifically documented data.

This accepted scientific/regulatory approach should be used by the Food and Drug Administration (FDA) to exert its ample enforcement authority to ensure safe and beneficial dietary supplements remain on the market.

It is by using this approach that we consider ephedra to be safe when formulated, labeled and used according the industry's voluntary ephedra program on manufacturing and labeling.

However, FDA has used a fragmented and inconsistent approach to its review of ephedra that undermines the accepted scientific/regulatory approach to ingredient safety. FDA appears to have selected information to include in the docket, blurred the case-by-case assessment by introducing irrelevant safety considerations about other sympathomimetics, and asked its consultants to come to a public health judgment based on partial data.

FDA appears to have selectively included information in the docket. The correct issue here is weight of all the evidence; the incorrect issue is selection of only some of the evidence. FDA reopened the ephedra record only a week ago requesting comment on the epidemiologic Hemorrhagic Stroke Project (HSP) study which addresses phenylpropanolamine (PPA). FDA entered only this study into the docket, and not -- even by reference -- the voluminous information and published and unpublished clinical studies submitted by CHPA over the years supporting PPA's safety. CHPA's recently submitted review on the HSP study was also not made available in the FDA docket. In fact, FDA's review of the pharmacology of ephedra alkaloids did not include most of the pivotal information on PPA we have submitted to the agency.

Given that FDA has entered other selected information on PPA into the ephedra docket, I would like to emphasize that, as with every ingredient safety issue, each individual AER and study must be considered in the context of the totality of the evidence on the ingredient. For PPA, the totality of the available evidence overwhelmingly supports the safety and effectiveness of PPA when used as directed on product labeling. This conclusion is based on approximately 40 clinical studies in over 3,000 subjects, including healthy volunteers and obese and hypertensive patients in single-dose and multi-dose regimens, as well as two supportive epidemiologic studies, all of which is detailed in our submissions to the OTC Docket on PPA. PPA-containing products have been used by millions of consumers over the past 50 years with a very low incidence of serious side effects.

But should the ephedra docket include certain safety information on other sympathomimetics? Let's remember that it is a case-by-case evaluation that should be the basis for public health decisions on ingredient safety. FDA's review of published literature includes 56 cerebro- and cardiovascular-related references, 34% of which related to ephedrine, the remainder to other sympathomimetic agents. The inclusion of large

amount of information on other sympathomimetic agents and the HSP study in the ephedra docket implies that an evaluation of the safety profile of other marketed sympathomimetics is important in the context of evaluating ephedra's safety. We do not agree this is the case, since (a.) the intended use of an ingredient is fundamental in its safety evaluation; (b.) different marketed sympathomimetics have different intended uses, based on their very well known and unique pharmacologic structure-activity relationships.¹ The fact is, while ephedra may include several sympathomimetic agents with different relative ratios of α and β receptor agonist activities, it is the mixture of these agents in the final ephedra product, not the activity of any one ingredient per se, that is relevant to the intended use or misuse of the product and a consideration of its safety. Hence, notwithstanding the fact that PPA is a minor component of ephedra, a partial review of PPA in FDA's report is also of limited value in the review of ephedra, and potentially misleading. Likewise, introducing the HSP study in the ephedra docket is also of questionable value, even if the study were of a quality to enhance our understanding of the safety of PPA.

On this latter point, there are serious limitations to the HSP study, but it is important to note that the HSP study did not establish a causal relationship between PPA and hemorrhagic stroke, and it collected no information on ephedra. As Dr. Charles Hennekens will directly follow me with a more detailed review of the strength and limitations of the HSP study, it should suffice for me to say that chance, bias and confounding are each plausible alternative explanations of the findings from this study. Thus, as a stand-alone study, the data from the HSP are not sufficiently informative to draw any firm conclusions, either about PPA or ephedra.

Another concern relates to FDA instructing three of its consultants to review a selection of AERs and determine whether ephedra is safe – i.e., to make an overall public health assessment based essentially on the AERs.

This direction from the agency was inappropriate.

- First, it is well recognized that, in general, AERs are individual reports, often lacking in important details or presenting details giving more likely explanations of the

¹ For example, PPA is considered to have predominantly α receptor agonist activity, while ephedrine has both α and β receptor agonist activities. This difference at recommended OTC dosages has led to different uses of these agents, with PPA used as a nasal decongestant where predominant α stimulation results in peripheral vasoconstriction and relief of nasal congestion associated with colds and flu. Ephedrine has α agonist activity, but it is its potent β_2 receptor activity that has led to its accepted use in OTC medicines for bronchodilation in the treatment of asthma. Ephedra has been used in traditional Chinese medicine for the treatment of asthma as well. The distinction in the principal receptor agonist activity at OTC doses (i.e., principally α or β), while important from the standpoint of intended use, is also important in relation to adrenergic receptor activation in other organs. For example (see also below), studies show that at recommended dosages PPA causes transient, but clinically insignificant, changes in blood pressure (i.e., due to α agonist activity and peripheral arterial vasoconstriction) with no change in heart rate (i.e., a β receptor related agonist activity). As a botanical, ephedra contains a number of constituents, including ephedrine as the principal active constituent, but also PPA and other sympathomimetics, the relative concentrations of which in the final product are subject to variations relating to growing conditions (e.g., seasonal effects), harvesting methods (e.g., choice of plant and plant parts), extract methods, etc.

reported event. As such, they are considered mainly as hypothesis-generating not hypothesis-testing data sets, certainly not rising in and of themselves to the level of scientific documentation needed for overall public health decision making.

The AER database on ephedra is inadequate with only a small subset of reports having sufficient detail for appropriate causation analysis. Different reviewers saw different sets of AERs, and among the three reviewers there were wide differences in opinions about the causation judgments relating to the individual AERs, showing the highly subjective nature of such analyses. A careful review of the AERs, as the Ephedra Education Council has done, shows the great limitations to this data set as a basis for any causality assessment supporting significant or unreasonable risk attributable to ephedra.

- Second, as mentioned, an important hurdle in coming to a public health decision about ingredient safety is the scientific documentation phase of the scientific/regulatory process. In this phase, all the relevant information must be gathered and evaluated for credibility and completeness before a public health judgment can be made. Therefore, FDA should have either given its consultants all the information or asked its consultants only about the nature of the scientific documentation of AERs. As a result, the conclusions reached by these consultants are necessarily limited, if not frankly in question.

Parenthetically, I might add that at least one of the FDA's expert reviews of AERs reportedly associated with ephedra placed pharmacologic plausibility as the top criterion of the attribution assessment. This biases the review against ephedra, since non-ephedra-related health problems can have an endogenous sympathomimetic component. By first deciding if the AER has a sympathomimetic-related course of events, sympathomimetic-mediated conditions can be falsely attributed to ephedra, and there is a tendency to not look for other more plausible explanations.

These concerns are important. FDA has approached its assessment of ephedra in a fragmented way, undermining the accepted scientific/regulatory approach that: evaluates each ingredient on its own merits; focuses on scientific documentation first; and relies on the weight of all the evidence. Important information on ephedra is still being developed by the industry, and this should be included in any assessment of ephedra before regulatory decisions are made.

Finally, CHPA member companies that market ephedra-containing dietary supplements have adopted a voluntary program for their ephedra-containing products relating to formulations and labeling, which has also been adopted by members of the American Herbal Products Association, National Nutritional Foods Association, and Utah Natural Products Alliance. The industry voluntary program was reviewed in previous presentations and includes the following provisions:

- Serving limits not in excess of 25 mg of total ephedrine alkaloids and not more than 100 mg per day;

- Label identification in conformity with the standard common name listed in *Herbs of Commerce*;
- Label listing of the amount of ephedrine alkaloids per serving;
- No synthetically derived ephedrine alkaloids or their salts either in finished consumer goods or in raw materials used in their manufacturer;
- No claims that the product may be useful to achieve an altered state of consciousness, euphoria, or as a “legal” alternative for an illicit drug;
- A label statement including the following elements or a statement in conformance with applicable OTC monographs:
 - Not intended for use by anyone under the age of 18. Do not use this product if you are pregnant or nursing. Consult a health care professional before using this product if you have heart disease, thyroid disease, diabetes, high blood pressure, psychiatric condition, difficulty in urinating, prostate enlargement, or seizure disorder, if you are taking a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).
 - Exceeding recommended serving will not improve results and may cause serious adverse health effects.
 - Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.

On balance, then, when formulated, labeled, and used according to industry’s voluntary program, ephedra-containing dietary supplements are safe. CHPA recommends that FDA adopt these industry recommendations into regulation.