REPORT OF EPHEDRA WORKING GROUP

to the National Advisory Council for Complementary and Alternative Medicine

The Ephedra Working Group met on Wednesday, February 26, 2003 in Rockville, Maryland. In preparation for that meeting, the panel was provided with a draft copy of the RAND report, as well as new publications since the preparation of the report. The panel was charged to identify avenues of potential research to expand knowledge of the risks and benefits of ephedra. In that context, the panel addressed four main areas: the current status of evidence regarding the safety of ephedra; the current status of evidence regarding the efficacy of ephedra for weight loss; the current status of evidence regarding the efficacy of ephedra for enhanced athletic performance; and the optimal study design(s) for addressing identified gaps in knowledge regarding both safety and efficacy.

I. With regard to the current status of the evidence regarding the safety of ephedra, the panelists concluded that:

1. It was clear from the RAND report that the data on safety of ephedra are currently inconclusive. The available data afford no basis for estimating the balance of risks and benefits of ephedra. Given the evidence currently available, however, there is no justification for the presumption of safety of ephedra. It cannot be demonstrated that ephedra is safe, nor can it be demonstrated that ephedra is not safe.

2. However, while the available data may be inadequate to definitively evaluate the question of safety, they are more than adequate to clearly send a signal of concern, which must be evaluated. The data from randomized trials are sufficient to indicate that the use of ephedrine or ephedrine with caffeine is associated with 2-3 times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations. The trials were not of sufficient size to evaluate even in aggregate the possibility of serious side effects that are rare such as death, myocardial infarction, strokes, seizures and psychiatric symptoms.

3. Information on these serious but rare events was available only from sporadic adverse event reports. It is important to note the limitations of these data in that they do not have information on denominators, and cannot demonstrate causality. Of most concern were the "sentinel" events, which were based on documentation that: 1) an adverse event had occurred; 2) the subject had consumed ephedra within 24 hours prior to the event or a toxicological examination showed ephedrine or one of its associated products in the blood or urine; and 3) an adequate investigation had evaluated for and excluded other causes. A total of 21 sentinel events were identified with prior ephedra consumption: two deaths, four myocardial infarctions, nine strokes, one seizure, and five psychiatric cases.* About half of all sentinel events occurred in persons aged 30 years or younger, although this could easily reflect patterns of spontaneous reporting.

4. To more rigorously evaluate whether consumption of ephedra is causally related to these serious but rare adverse events requires an analytic epidemiologic study design, such as a case-control study.

II. With regard to the current status of the evidence regarding the efficacy of ephedra for weight loss, the panelists concluded that:

1. Few trials of ephedra have been conducted. However, taken together, the evidence suggests that short-term use of ephedrine, ephedrine with caffeine, or dietary supplements containing ephedra with or without caffeine, is associated with short-term weight loss of approximately 2 pounds per month, compared to placebo. However, panelists with extensive experience evaluating other weight loss agents noted that little is known about how ephedra is used by the public, in terms of factors that could potentiate the success of any dietary supplement, such as concurrent dietary changes, exercise, or counseling. As a result, the reported studies that included these components are likely overestimating the effects of ephedra as it would be used by consumers, and thus many would not achieve this degree of weight loss with ephedra.

2. No evidence exists as to the dose-response relationship.

3. No evidence from controlled trials exists as to whether continued use of ephedra would result in long-term (>6 months) weight loss or weight loss maintenance, or influence clinical health outcomes as distinguished from cardiovascular disease risk factors.

III. With regard to the current status of the evidence regarding the efficacy of ephedra for athletic performance enhancement, the panelists concluded that:

1. There are no clinical trials of ephedra for athletic performance enhancement.

2. There are no clinical trials of chronic use, even of ephedrine, for performance enhancement. Available trials have assessed effects of acute dosing on very short-term immediate performance (1-2 hours after a single dose) among very fit individuals.

3. There has been limited replication of the findings with regard to ephedrine, with virtually all reported trials having emanated from a single laboratory.

4. Virtually all trials of ephedrine have been conducted on a small number of very fit young men (athletes, military recruits), limiting generalizability of the findings.

5. The available data support a modest effect of ephedrine with caffeine on very short-term indicators of athletic performance enhancement, such as time to exhaustion, increase in performance time, and power output.

6. In reviewing reported cases of ephedra use, no information was provided on factors such as: patterns of actual use of ephedra by the general population to enhance athletic performance, including concomitant use of medications such as anabolic steroids; effects of different environmental conditions such as humidity and hydration; effects on blood pressure and arrhythmic effects (observed increase seen in exercise heart rates with ephedrine); effects of thermal stress plus exercise stress; and effects of sustained use on performance over time.

IV. With regard to the next steps in terms of research on ephedra, the panel agreed that a portfolio of research options should be recommended.

1. The Ephedra Working Group made the clear and strong recommendation that NIH, NCCAM and ODS must consider dealing with the safety of ephedra as its first priority. Given that the young represent a vulnerable population in whom assessing risks are of greatest concern, the panel recommended that the first step of any research portfolio should be a case-control study conducted among adolescents and young adults using ephedra for performance enhancement. "Cases" in various such studies could include ischemic vascular events, and/or cardiovascular events, and/or heat stroke. Not only would a case-control study be the optimal study design to evaluate these rare events, but the lack of substantial co-morbidity in this group would make it easier to judge the existence of a cause-effect relationship, as compared with the co-morbidities present in obese women using ephedra for weight loss. While the rigorous scientific design of such a case-control study would involve careful consideration of a number of epidemiologic issues, it would allow the evaluation of the safety of ephedra use among the young in a cost-efficient and timely manner.

2. While such a case-control study is ongoing, a number of other research avenues to evaluate safety and efficacy could be pursued, which would take varying lengths of time to complete and would concurrently address many of the current gaps in knowledge concerning ephedra. These include:

   a) The initiation of surveys, or the piggy-backing of questionnaires onto ongoing cohort studies, in order to elucidate the current patterns of use of ephedra, including dose and use of concurrent medications, as well as the characteristics of the users. This would also allow initiation of prospective follow-up of self-reported users. Such information would provide critical pieces regarding the numerators of events and denominators of use, information that would inform the design of future studies.

   b) The conduct of basic research investigations, including pharmacokinetic drug interaction assessments (including identification of particular vulnerabilities and interactions with agents such as anabolic steroids or sympathomimetics), and experiments that examine physiologic responses under such conditions as exercise and thermal stress.

   c) The conduct of clinical trials to evaluate the safety and efficacy of ephedra for weight loss among overweight and obese women and men. The first part of this research would consist of a Phase II study, evaluating adverse effects, weight loss, and physiological responses, as well as optimal dosing. The next step would consist of a randomized clinical trial of adequate sample size to characterize side effects and evaluate efficacy with regard to moderate or long-term weight loss, weight loss maintenance, and relevant health outcomes. The panelists emphasized that for any clinical trial testing, the study design would have to control for the quality of the active ingredient in the accurate amount, an effort that would require standardizing the products and determining the right dose to be used for testing.

V. Comments

The panel emphasized that there was not going to be a quick or inexpensive way to answer the ephedra questions of safety and efficacy definitively; that one study could not provide all the answers; and that it would take a portfolio of research approaches. While the panel members were clearly cognizant that their charge was not to advise on the regulatory aspects of ephedra, but only to identify potential research opportunities to expand knowledge, they felt the situation with ephedra was directly analogous to that seen in the development of any new drug, while recognizing that it is a complex botanical product. Finally, deciding how to invest precious NCCAM, ODS, and NIH resources in answering public health questions is always a difficult issue. While evaluating the safety issues of a product being widely used is an overarching priority, the panelists felt a decision to invest significant portion of NCCAM's research dollars in establishing the efficacy of ephedra and ephedra-containing products as weight loss tools would involve the weighing of competing research priorities.

*The Ephedra Working Group reviewed a draft copy of the RAND report in preparation for the meeting on February 26, 2003. The final document, released on February 28, 2003, reports a total of 22 sentinel events identified with prior ephedra consumption: two deaths, three myocardial infarctions, nine strokes, three seizures, and five psychiatric cases.