DR. HACKMAN: People do come to me with concerns about sleeplessness and jitteriness primarily. I advise them the same thing that is on the label, to discontinue use.

The informal recordkeeping that I have as to how many negatives to positives, I would estimate to be maybe one to 10 negative or adverse events to positives. But I do not keep a written log of that, so it is only my best estimate.

DR. COATES: Thank you.

DR. JONES: Further questions from the panel?

[No response.]

DR. JONES: Questions from the floor?

[No response.]

DR. JONES: Being none, thank you, Dr. Hackman.

Dr. Fomus from the Council for Responsible Nutrition.

DR. FOMUS: Good morning Dr. Jones, distinguished panel, ladies and gentlemen. My name is Kathy Fomus from the Council for Responsible Nutrition and I am substituting for John Cordero.

Mr. Cordero regrets that he cannot personally deliver these remarks, however,I am pleased to be here in his place.

The Council for Responsible Nutrition was founded in 1973 and represents more than 110 companies in the dietary supplement industry. CRN members adhere to a strong code of ethics and comply with self-regulating dosage limits had label warnings.

CRN's member companies manufacture dietary supplements to high-quality standards under CRN's good manufacturing practices which were adopted in the mid 1980s.

CRN has been actively involved for about seven years with the Food and Drug Administration, other associations and the scientific community in the evaluation of the scientific evidence and policy options for ephedra. Over the last two years or so efforts to resolve issues on safety, dose, and duration have bogged down. Coming to a head with a General Accounting Office report criticizing FDA's procedures and evaluating ephedra.

CRN which prides itself on adherence to scientific evidence took the GAO analysis very seriously and contracted with the prestigious and experienced CANTOX Health Science International to perform a quantitative risk assessment. In addition to the CANTOX risk assessment there is a major new clinical trial by Columbia and Harvard Universities

that is pending publication.

In a letter to Mr. Joseph Levitt, Director of FDA's Center for Food Safety at Applied Nutrition CRN called FDA's attention to the Columbia/Harvard clinical trial as well as the CANTOX risk assessment. Noting that neither report would be available for detailed discussion today, CRN's letter urged a delay in policymaking until these studies could be carefully considered in a fully transparent matter.

Given that these will be two of the most comprehensive studies of there types on ephedra, it would see that they are necessary for credible scientific conclusion on which policy might be based.

Upon completion these reports should be subject to scrutiny in a public forum. FDA is urged to convene a follow-up meeting to allow public discourse on these studies before reaching any conclusions on ephedra.

I would like to take a few moments to describe this emerging evidence. First, the clinical trial conducted by Columbia and Harvard universities. This trial has been completed, the data are being analyzed, and tentative plans have been made to report to results at a conference at the end of October.

This study is one of the largest and longest

duration clinical trials conducted on ephedra. Additionally it examines the impact of ephedra on a large number of health indicators. A preliminary trial has already been described in a published abstract.

In a letter to FDA, Dr. Carol Boozer of Columbia University, and one of the principal give investigators, explained the status of this study and its importance in evaluating ephedra. Given the quality, size, and duration of this clinical trial, it would be premature, unjustifiable, and a public disservice for FDA to reach conclusions on ephedra without waiting for the availability of this data.

Second, as I mentioned earlier, CRN has contracted with CANTOX Health Sciences International for a formal risk assessment of ephedra as a dietary supplement. CRN has publicly presented the design and methods of this assessment and has briefed FDA staff on it as well.

Following this presentation my colleague, Dr. John Hathcock, will describe the merits of a formal, structured, risk assessment, citing the uses and impacts of the different types of evidence available. CRN believes that FDA should carefully examine the results of the CANTOX risk assessment before reaching scientific conclusions on the safety of ephedra.

This will be the first risk assessment carried out completely in accordance with a set of procedures and guidelines identified in advance using the tolerable upper intake or UL protocol developed by the U.S. National Academy of Sciences. In contrast to FDA's rush to judgment, CRN's evaluation of the science relevant to the safety of ephedra will embrace the totality of available evidence including the Columbia/Harvard data.

As we all know, the scientific evaluation process that FDA used in an attempt to justify its 1997 proposed rule was strongly -- and I believe accurately -- criticized by GAO. These criticisms led FDA to withdraw most of that proposed rule. CRN strongly recommends that FDA not repeat the mistake of drawing premature and unjustified scientific conclusions as it did in developing its 1997 proposal.

Instead CRN urges FDA to use a deliberate, careful, and fully transparent public procedure of scientific assessment so that its future policy position on ephedra, if any, will be fully justified and defensible.

Thank you for your attention. I defer the remainder of my time to my colleague Dr. Hathcock who will speak next and questions will be addressed at the

end of his presentation.

DR. JONES: Thank you, Ms. Fomus.

Dr. Hathcock. I am timing you for 15 minutes. Just to be clear, I had not been given to understand in advance there was any negotiation of time or anything. So 15 minutes.

DR. HATHCOCK: I believe I can accommodate that.

DR. JONES: Thank you.

DR. HATHCOCK: Thank you, Dr. Jones. Good morning to you and the panelists. The title of my presentation is, risk assessment, an application of criteria for causality to ephedra AERs. The risk assessment is nothing more and absolutely nothing less than a systematic, quantitative evaluation of the potential for a substance to produce adverse effects. For risk assessment to be objective and avoid bias it is crucial that it be performed under an established model, a set of clearly identify procedures and criteria. It is equally important that the risk assessment model to be used with its built-in objective procedures and criteria be selected in advance.

Unstructured reviews and evaluations are extremely subject to biases of the reviewer. Excuse me for a moment.

The objective of a risk assessment reflects the policy intent behind the decision to use this procedure. Depending upon the scientific evidence available, risk assessment can answer a range of questions. For example, questions which it may answer are given in the following examples.

Is this substance toxic at any dose? According to Paris Solis some 500 years ago that one is a foregone conclusion.

Another question might be, does a specific daily does say 00 milligrams produce adverse effects? Another question might be, what is the highest dose that is unlikely to cause adverse effects? Clearly that was the objective of our risk assessment as we will see.

Also the appropriateness of our risk assessment model to deserves some clarification. Risk assessment has been most commonly applied to environmental chemicals that include additives. For example the acceptable daily intake or ADI method commonly applied to food additives uses large safety factors sometimes called uncertainty factor usually 10 or 100. EPA's reference dose model commonly applied to environmental chemicals in pesticide residues in food, considers five types of uncertainty, with each being

assigned a standard default uncertainty factor of 10, 3, or 1.

Thus the final composite uncertainty factor in the reference dose model can range from 100,000 down to 1. The most commonly selected composite factors though, however, are 10, 30, 100, and 300.

In recent years there is a strong movement in the science of quantitative toxicology toward risk assessment models that utilize uncertainty factors that are fully derived from the specific database, thereby avoiding all arbitrary default values.

The U.S. National Academy of Sciences Food and Nutrition Board is a leader in this movement. Under financial sponsorship largely from FDA, a subcommittee of the Food and Nutrition Board developed and published its tolerable upper intake level or UL model for application to nutrients. The UL method was a good idea because it is less objective and arbitrary than other methods. It uses better science than the other methods is that it derives the uncertainty factors directly from the database. This approach was necessary because the standard default uncertainty factors such as in the ADI and RFD methods often generate nonsensical answers when applied to nutrients.

Illogical answers such as the safe intake

being below the RDA often occur because the range between the intakes that are nutritionally useful and the possibly adverse level are less than 10 for some nutrients and less than threefold for a few.

In effect, the UL method recognizes that vitamins and minerals are deliberate, intentional, and desirable components of the human diet.

CRN chose the UL risk assessment model for application to ephedra for several reasons. First, the uncertainty factors are fully derived from the database. Second, it acknowledges that ephedra is a deliberate ingredients of dietary supplements. And, third, it addresses the totality of the scientific evidence -- all types of scientific evidence.

CRN's objective in applying the risk assessment model was straightforward to identify the highest daily intake that is likely to posed no threat of adverse effects to almost all individuals in the healthy population. The U.S. National Academy of Sciences UL model with all of its built-in definitions, procedures, and criteria, and obligations together with application by a neutral third party was selected to avoid bias. Perhaps that is enough on the principles of risk assessment.

Now I would like to address the AERs, what

they are they are not; what they mean and what they do not mean; how they should be used to and how they should not be used. And, finally, how they fit into risk assessment and how they do not fit in.

To evaluate AERs all other types of data on the human health impacts of any substance it is useful to examine the criteria for causality originally developed in the context of environmental medicine but were recently adapted and incorporated into the U. S. NAS -- by the U. S. NAS model for risk assessment.

The criteria include strength of the association, consistency of the association, specificity of association, the temporal relationship, the dose response relationship, biological plausibility, and overall coherence. A body of evidence from several well-designed and conducted clinical trials can measure up strongly against most of these criteria because each factor can be controlled.

Epidemiological studies often prove weak against one or more of these criteria especially the strength, consistency, and specificity factors. Congruence of biological effects it epidemiological studies were those observed in animal studies and clinical trials can increase the confidence in the data.

AERs must not be overinterpreted. Of course there is a tendency to do this if the effects of biological are plausible and the relationship is temporally logical. Biological plausibility and temporally correct relationships however can never prove causality.

Some ephedra AERs passed these two criteria but fail against others. An important consideration is this: there is no need to overinterpreted and depend on AERs is to reach scientific conclusions when there is a sufficient body a evidence of a vastly superior type mainly clinical trial data. Indeed, under these circumstances no decision should be made primarily or solely on the AERs. Instead the only logical way to do a risk assessment on ephedra or any other substance for that matter is to consider the totality of publicly available scientific evidence.

Here it is interesting to note that the Nutritional Label and Educational Act demands precisely that approach in deciding whether a health claim can be authorized by FDA. It demands consideration of the totality of the scientific evidence.

Likewise, any risk assessment on any substance should consider the totality of the evidence. With regard to the scientific meaning of AERs it is

noteworthy that a disclaimer box appears on the screen whenever one searches the FDA's Center for Food Safety and Applied Nutrition web site for AER associated with any product. This disclaimer acknowledges in slightly different words that AERs cannot demonstrate causality. The FDA disclaimer includes the following points:

There is no certainty that a reported adverse effect can be attributed to a particular product or ingredient. The total number of adverse events cannot be used to estimate the rate of the adverse event to the population. A reporting of adverse events may be affected by several factors including time in the market and publicity. With this acknowledged limitation on the meaning and significance of the AER it is surprising to see that most of FDA's actions on ephedra have been based primarily on the AERs. If the AERs are flawed what information then can they provide and what information can they not provide? And, finally, what information have they provided about ephedra?

AERs are simply reports by persons who believe that an adverse event may have been caused by a product. The publicly available AERs on ephedra range in size from less than one page to approximately 500 pages. It is easy but quite fallacious to assume that

an AER of hundreds of pages must provide convincing evidence that would pass the causality criteria.

Clearly from my examination of them, most of the detailed AERs spend most of their attention in a very detailed characterization of the adverse events and in establishing the person actually took a product containing ephedra. The following false rationale seems to be employed if a person took a product and had an adverse event that is plausible for ephedra, then ephedra is likely to have caused it. It seems to be that simple, but it is fallacious.

If that line of thinking had any validity defensible scientific conclusions and policy decisions would have long since been reached and we would not be here today.

Many of the AERs do not contain information that would shed any light on the specificity of the association. Many of the AERs do not contain product information. Many of the AERs that do contain some product information are nevertheless hopelessly confounded by congruent consumption of other substances that carry equally convincing biological plausibility and with the same temporal relationship.

For ephedra all other stimulants can confound interpretation of an AER. Examples of confounding

stimulants include the OTC drugs containing ephedrine, pseudoephedrine, and other similarly acting compounds, caffeine and other methylzanhthines from OTC drugs, nicotine and a wide variety of foods and beverages contain one or more of those ingredients.

Also and AER can be confounded by pre-existing medical conditions that not only could help contribute to a reaction to ephedra, but also could have been the primary or perhaps the only cause of the event. One AER in particular provides an excellent example. A middle-aged man somewhat overweight drank coffee, took an ephedra supplement, what jogging, and died of a heart attack. We have heard this one discussed already.

Post-mortem examination showed that his two largest coronary arteries were more than 75 percent closed by atherosclerotic plaque. Did the jogging contribute to the heart attack? Did the caffeine cause or contribute to it? Did he ephedra clause or contribute? Would it have happened anyway? The only scientifically defensible answer is this: nobody knows. I wish we did, but we don't. And there is no way to analyze AERs to avoid such uncertainties because the best documented AERs simply do not provide all the needed information.

If the individual AERs cannot support a cause and effect conclusion does the number or pattern of AERs on ephedra provide sufficient information? As anyone might wish to that that were true, the answer is a firm no. Whether causally related or not, and nobody can tell, the number of AERs would be expected to increase with the length of time in the market and the number of people using the product.

The number of ephedra AERs per year has varied with a much stronger temporal relationship to publicity from FDA than to increases in sales. If the accumulated AERs nominally related to ephedra have no identifiable meaning, could well documented AERs show cause and effect? Unfortunately, the answer is no.

AERs alone can never answer this question; what is the rate of identical adverse events in a similar population who did not consume the product?

A large body of well-documented AERs adds up to not much. Precisely what it does add up to it is one-half of a case controlled study. The controls are missing.

Even if the study were completed with inclusion of appropriate controls it would still be an epidemiological study and would pale in comparison with a greater meaning of controlled clinical trials.

In summary, the criteria for causality adopted by the National Academy of Sciences demand that we pay a greater attention and depend primarily on clinical trial data instead of AERs and excessive risk on ephedra. The only time to AERs should dominate the evaluation is when they are the only evidence available and when other evidence cannot be ethically obtained.

In general, AERs should be used in as a flag to identify areas for additional research.

To reiterate comments made by my colleague, Dr. Fomus, a few moments ago no scientific conclusions on ephedra should be reached until the data from the forthcoming Columbia/Harvard study -- clinical trial are available and can be evaluated through a public process. But with or without those new data any safety evaluation of ephedra should depend strongly on the substantial available evidence from clinical trials and not from the inherently insufficient AERs.

Thank you for your attention, I look forward to questions.

DR. JONES: Thank you, Dr. Hathcock.

I would presume you and Dr. Fomus would take questions together. I appreciate your combining your time. Questions from the panel, Dr. Coates.

DR. COATES: Dr. Hathcock and Dr. Fomus, I

will not ask you about the status of the clinical study to which you referred, I suspect we will get some more information about that from the principals.

DR. HATHCOCK: I hope so.

DR. COATES: But could I ask you what the status is of the quantitative risk assessment that you have done in collaboration with CANTOX and when approximately can one expect to see results?

DR. HATHCOCK: We have received a preliminary draft. We are not making the results of that public because we believe that it would be an improper thing to do to issue even tentative conclusions in the face of the new major forthcoming evidence that might cause a major revision. We believe that the impact of the Columbia/Harvard study will be to greatly increased the confidence that we have in the data that would either decrease the uncertainty factor or change the new observed adverse effect level.

DR. COATES: Could I follow up? The quantitative risk assessment as you have described it is based on what you have said is the totality of evidence; does that include unpublished clinical trials and other clinical studies? Or does it -- is it restricted to the published peer reviewed literature? And so I guess the question you can anticipate is, if

the Columbia/Harvard study is at a certain stage well then its publication dictates the publication release of the results of the Q&A?

DR. HATHCOCK: We are including in the risk assessment all data that are publicly available whether they are peer reviewed or not, and that is clearly identified whether they are or not and that can be taken into account and others judging the validity of the process. But if and when the appropriate data and details of methodology are released, whether or not it's in a peer reviewed paper, we will cite that source and acknowledge the status and proceed.

DR. JONES: Dr. Philen.

DR. PHILEN: My questions were primarily about the study, so if perhaps somebody later on is going to be better prepared to answer it, I will just wait.

DR. HATHCOCK: About the clinical trials --

DR. JONES: We do have a presentation.

DR. HATHCOCK: -- I understand that Dr. Boozer is on the program and --

DR. JONES: Yes, Drs. Boozer and Daly.

DR. HATHCOCK: -- I would not presume to preempt her.

DR. JONES: Very good. Dr. Salive.

DR. SALIVE: Marcel Salive, NIH. You have called into question any adverse event reports that are confounded by anything. I guess I have a question. I mean, are you calling into question the other ingredients in the product as a confounding issue? Because to me that is really begging the question considerably if the products are not a pure synthetic product, there are going to be multiple ingredients like we heard yesterday and so they all have some effects all the body obviously.

DR. HATHCOCK: What I am doing is saying that when you look at a published case report or series of case reports, or clinical trial, or a pharmacokinetics study, or animal study, or whatever, you apply the criteria for causality. Going through those then with AERs you are forced to apply those to one case at a time. Many of them are going to fall out because, well, a temporally incorrect relationship in the reverse direction makes it nonsense of course. If there is a major confounding by pre-existing condition or concurrent consumption one has to take that into account in determining whether there is likely validity to the report.

The overall analysis of AERs so depends on doing all of those and then seeing what's left. I am

not saying that we totally throw out anything that is even slightly confounded that one person drank one cup of coffee per day would that be considered confounded and likely not, but that is my judgment.

DR. SALIVE: Okay. A follow-up question is if that is, the case then you are saying also you would consider pre-existing conditions a confounding issue?

My reading of the trials that have been done so far there are many exclusionary criteria for pre-existing conditions and so even the clinical trials do not provide any data on safe use of the product in people with pre-existing conditions of which there are a fairly large number in the country who may be interested in taking the product and want to know about the safety profile, you know, that might be relevant to them; how could that information be obtained?

DR. HATHCOCK: Ultimately and under the National Academy's UL model, they have provisions for evaluation of subpopulations. Good data on subpopulations is helpful. It is necessary to really make any judgments other than speculative judgments.

If one concludes though that you want to remove any possibility of an adverse effect based on a pre-existing condition or a sensitivity that has not yet been documented there is no end to that. The only

acceptable -- if the only acceptable risk is zero, then there is no way to go to any possible use of the product. I do not believe this is warranted and certainly the National Academy model recognizes that certain subpopulations simply have to be removed from consideration such as they have not published on this yet, but I can imagine that they will conclude that on -- relationship thenalanine intake. I imagine that they will reach that conclusion on Wilson's disease patients in relationship to copper intake. I published on this a couple of times and if you set a copper limit based on Wilson's disease subjects you are going to have a level that is deficient for everybody else.

DR. JONES: Thank you. I see one question from the floor. If there are other questions, please get to the microphone. Please go ahead, sir.

MR. MOWERY: Dan Mowery from the American Phytotherapy Research Laboratory. I have a couple of questions about the funding of the studies if possible. We know that under Douche the burden of proof ultimately rests with FDA on some of these issues. Are any other funds for the studies these studies that we referred to today coming from FDA or from a government source?

DR. HATHCOCK: I am not certain. I think I

know, but I am not certain, and I would prefer that the funding about the Columbia/Harvard study be answered by the principal investigator. That would be speculation for me to preempt that.

The UL model development was funded by FDA principally through the National Academy. Its application on ephedra was funded by the Council for Responsible Nutrition and we, as Dr. Fomus said, we are a trade association representing manufacturers.

DR. MOWERY: Are you aware of any other studies being conducted now besides the ones that you referred to on ephedra or ephedrine for that matter or ephedrine caffeine?

DR. HATHCOCK: Since that is asking for an awareness, maybe some of our federal colleagues up front here could answer. Are you aware of questions -- I mean, of studies of ephedra being funded by the federal government?

DR. JONES: It looks like the answer to that is a no. Thank you.

DR. HATHCOCK: My answer was that I was not.

DR. JONES: Colonel Myers.

COL. MYERS: Colonel Ester Myers from the Air Force. How will you address in your analysis the departure from one of the major premises of the

National Academy of Sciences which is to rely only on peer reviewed data?

DR. HATHCOCK: We are relying principally on peer reviewed data but we are also analyzing the AERs which are not peer reviewed. We all or acknowledging the status, peer review, or otherwise so the criteria -- scientific criteria being applied are there except for peer review and we are acknowledging whether or not the source was peer reviewed. But of course, all AERs fit in that category of non-peer reviewed data.

DR. JONES: Thank you. Thank you very much, Dr. Fomus and Dr. Hathcock.

We proceed now to Mark Blumenthal of the American Botanical Council.

DR. BLUMENTHAL: Good morning, Dr. Jones, members of the panel, audience. I am Mark Blumenthal, founder and Executive Director of the American Botanical Council, a nonprofit research and educational organization in Austin, Texas, founded in 1988.

ABC is an organization of the scientists interested in research and education on medicinal plants, herbs and phytomedicines and the dissemination of accurate responsible science-based information on these materials.

ABC is a nonmember-based organization and is

neither a consumer organization or a trade association but consistently deals with research, market, and regulatory issues about herbs and phytomedicines, issues of concern to consumers health care practitioners academia, industry, and regulators.

ABC receives financial support from the general public, from the sale of educational materials and from donations from individuals, foundations, and members of the business community including both herb and pharmaceutical industries.

I have received no direct consideration or support from any member of industry for my expenses and appearance at this hearing.

By way of introduction, as part of my role at ABC, I am also the editor of Herbal Gram, a peer reviewed quarterly publication on herbal research, market issues, and regulation, and that has covered these subjects since 1983. I am also the senior editor of a book called: The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicine, and senior editor of a follow-up publication, Herbal Medicine: Expanded Commission E Monographs, published this year.

Finally I also served as an adjunct associate professor of medicinal chemistry at the College of

Pharmacy at the University of Texas at Austin where I teach a course it herbs and phytomedicines to fifth-year of pharmacy students.

I am most grateful for the opportunity to testify at this hearing. My goal is to contribute to a rational view of the herb ephedra as it has been reported previously in articles published in the HerbalGram, plus additional information from the monographs of ephedra produced by ABC into two books cited above. These books are based on the evaluations conducted on herbs and phytomedicines in Germany by the esteemed Commission E, an expert panel of physicians, pharmacologists, and pharmacists of the German Federal Institute of Drugs and Medical Devices, an agency analogous to the U.S. Food and Drug Administration.

The Commission E evaluated all of the available scientific and medical literature that had been published on ephedra and its alkaloids up to and around 1990 and formulated a monograph to be used as a package insert for ephedra products sold as nonprescription drugs in German pharmacies.

ABC is well aware of the concerns being expressed by various members of the public, organizations, and regulatory bodies over the potential risks involved with the use of this herb in dietary

supplements in the U.S. During the past five years HerbalGram has published at least 12 articles documenting the use and misuse of ephedra, the research on this herb, and its regulatory situation. In addition, we have published both the Commission E monograph and the expanded version and we are currently completing a more thorough literature review and assessment of clinical and therapeutic literature on ephedra for a series of monographs we are producing for continuing medical education for health-care professionals.

The Commission E monograph published in January 1991, limits the approved use of ephedra to "disease of the respiratory tract with mild bronchospasms in adults and children over the age of six." Of course, the contraindications, side effects, and herb-drug interactions are also mentioned, consistent with those already noted in various presentations during this hearing.

Of probable interest to you, however, as members of the expert panel is the dosage that Commission E has set for ephedra which I give you now:

Single doses and single dosage form for adults are "herb preparations corresponding to 15 to 30 milligrams total alkaloids, calculated as ephedrine."

And for children, herb preparations corresponding to 0.5 milligrams total alkaloids per kilogram of body weight. The maximum daily dosage for adults according to Commission E is 300 milligrams of total alkaloids per day; for children it is two milligrams total alkaloids per kilogram of body weight.

The duration of use for this relatively high adult does is held to short-term use for the indication as just mentioned.

In the second book cited about herbal medicine: expanded Commission E monographs, we have added additional dosage information and numerous references to the primary and secondary scientific literature. I have provided copies of these monographs and the articles from HerbalGram for your possible future reference and for the record.

In reviewing the available medical and ethnobotanical literature for the preparation of the monographs on ephedra, we noted that despite considerable documentation in the ethnobotanical literature, from traditional Chinese medicine, there are few published clinical studies on this herb, most research having been conducted on isolated ephedra alkaloids already cited here, usually ephedrine and pseudoephedrine, or some Chinese herbal combinations of

ephedra with other herbs, but not singly.

We are aware of at least for clinical studies on the herb ephedra not including the Harvard/Columbia study being referenced earlier. The first, White et al, 1997, dealt with the effects of powdered ephedra herb capsules in 375 milligrams capsules containing approximately a total of 26 milligrams of total ephedrine alkaloids. Conducted on 12 normal tensive adults between the age of 23 to 40. Although the authors concluded that "pharmacodynamic aspects of ingestion of ma huang in a normal tensive, young population was fairly benign," they also cautioned about the use of ephedra with other stimulants in high doses.

The trial small size is an obvious weakness, indicating the need for further large-scale studies.

The second trial, Nasser, et al, 1999, conducted at the Obesity Research Center, St. Luke's-Roosevelt Hospital Center, at Columbia University in New York, has not been published in a peer reviewed journal, at least not into our knowledge. We found the abstract in a FASEB publication in 1999. This trial dealt with thermogenesis using a commercial combination of herbal ingredients including ma huang called Metabolife 356 in an eight-week trial on 48

healthy subjects. The total daily intake was 72 milligrams of ephedra alkaloids with 240 milligrams caffeine.

Of the 48 people completing the trial out of 67 that had initially been randomized, 24 using this herb combination had greater weight reduction versus the placebo, lower percentage of body fat and lower serum triglyceride levels. The authors concluded that the herbal formula promotes weight loss but may also produce undesirable side effects is some subjects, noted as dry mouth, heart palpitations, changes in blood pressure, and insomnia. Because the study does not appear to have been peer reviewed, we are not certain about what conclusions can be drawn.

Gary Huber, M.D., of the Texas Nutrition Institute, has conducted to recent clinical trials which are currently in press which I believe he will discuss this afternoon during the hearing. We welcome his efforts to conduct clinical trials on preparations containing herbal material, not merely the isolated ephedrine-type alkaloids. As has been pointed out in this hearing and elsewhere, these ephedra dietary supplements are not single ingredient products -- they are chemically complex mixtures. Thus, it is important that ephedrine and related alkaloids not be viewed and

unassessed in a vacuum.

Direct comparisons to the herb ephedra and evaluations of the herb should be made. It ABC welcomes additional properly designed clinical trials that might provide more data about the potential benefits and potential risks of the herb ephedra.

ABC also believes that dietary supplement products containing ephedra should remain on the market and that they may be required to be manufactured according to proper good manufacturing practices and we welcome FDA's hopefully eminent publication of final regulations in this matter. And these products should be sold in reasonable dosage levels as already proposed by the American Herbal Products Association.

Also, these products should be labeled with appropriate warnings, consistent with the label warnings issued by AHPA in 1994 and subsequently revised, plus other relevant policy from AHPA, as presented by Michael McGuffin at this hearing yesterday afternoon.

Just as OTC drug products containing a ephedra-type alkaloids are sold to be used "only as directed," we believe similarly that most consumers would adhere to appropriate label directions and warnings. In addition, we believe a consumer education

campaign should be conducted that presents potential risks and potential benefits and well-documented benefits in a reasonable and impartial manner.

Finally, I present a brief statement from a member of the ABC Board of Trustees, Professor Varro E. Tyler, Dean and distinguished professor of Pharmacognosies Emeritus at the School of Pharmacy at Purdue University. Prof. Tyler is well-known in the United States as a leading advocate of rational herbal use. He was the author -- senior author of four editions of the textbook Pharmacognosy and is the author or co-author of several leading books on herbal medicine. He was also the vice president for academic affairs at Purdue and Dean of the School of Pharmacy for 20 years.

Dr. Tyler says, "in general, ephedra is safe but should not be used more than about 125 to 150 milligrams of alkaloids per day, 25 milligrams at four to six times per day dosages. Before taking it, people should be careful that they are not one of the people with the contraindications noted in label warnings. Is someone contemplates going on an ephedra diet, they should first be checked out by a physician before doing so and monitored during the period of the diet. If caffeine is going to be used in any form during the use

of ephedra, the dose of ephedra probably should be lowered."

By lower amounts, Prof. Tyler told me that he believes that 100 milligrams per day appears to be a reasonable dosage as it would constitute a 20 to 33 percent reduction from the recommended maximum that he says is 125 to 150 milligrams. Also this 100 milligrams represents a 66 percent reduction in the maximum allowed for short-term acute purposes by the Commission E.

Those are my comments. Thank you for your time and attention. I will be happy to answer any questions if I can.

DR. JONES: Thank you very much, Mr. Blumenthal.

Questions from the panel? Dr. Salive.

DR. SALIVE: Marcel Salive, NIH. When you recommend a consumer education campaign based on well-documented evidence, what are you referring to? Could you outline it a little bit?

MR. BLUMENTHAL: Thank you. I would like to qualify that. To my knowledge, there is not sufficient, well-documented evidence to develop a well-sought out consumer education campaign as far as the potential benefits all of ma huang and the risks

and therefore that would have also to be subjected to waiting for proper clinical trials to be conducted and published, hopefully those been conducted by Dr. Huber and the ones that are from Columbia/Harvard might constitute sufficient documentation.

We believe that peer reviewed scientific evidence, in addition to the ethnobotany, in addition to the pharmacology, in addition to the AERs, as a properly evaluated are part of a rational basis for conducting a campaign. But we believe that well-controlled clinical trials would have to be part of that and right now we believe that the evidence is to the scanty for that at this point.

DR. JONES: No other questions from the panel.

Dr. McLaughlin.

DR. McLAUGHLIN: Yes, Mark, the answer I gave to the question about the 12-week limitation for the duration of taking ephedra products was a speculative answer. I wonder if you can -- probably should be discounted if you can give us a better answer to that. Where did the 12 weeks come from?

MR. BLUMENTHAL: As I remember, several years ago, the state of Ohio was contemplating banning ephedra products and making them prescription only and