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# FOOD ADVISORY COMMITTEE

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Guest Participant:

Lester M. Crawford, Ph.D., D.V.M.

Guest Speakers:

Cynthia T. Culmo, Ph.D.
Frank Wickham
Micheline Ho

P A R T I C I P A N T S (Continued)

FDA Staff:

Dr. Elizabeth Yetley
Margaret Binzer, Office of Special Nutritionals
Constance Hardy, Office of Special Nutritionals
Dr. Bill Obermeyer
Louisa Nickerson, Office of General Counsel
Debbie Bowen, OTC Drug Staff

C O N T E N T S

P R O C E E D I N G S

DR. ASKEW: Good morning, ladies and gentlemen. Welcome to the meeting of the Food Advisory Committee for the Center for Food Safety and Nutrition. Today we are convening to carry on further discussion with regard to the potential health and safety problems that are associated with dietary supplements and other food products containing botanical ingredients that are sources of ephedrine alkaloids.

This is a meeting of the full Committee on Food Safety, augmented by a number of consultants selected by the FDA to assist us in our discussion of this matter. Earlier there was a working group meeting that considered this topic, and many of you here attended the working group meeting. We're going to have a review of the deliberations of the working group meeting. It is going to be brought before the entire committee. The entire committee then will consider this plus other new information that has developed and have a discussion of this topic.

In general, what we're going to do is, for those of you that have a copy of the agenda, we're going to have a review of the proceedings that went on with the working group meeting, and then we'll have opportunity for questions by committee members that weren't there. Then we will go

into open public hearing, take a break and come back, and have more open public hearing. We have a number of people that wish to comment. People will be limited to seven-and-a-half minutes.

Then we'll have an update from several people, including people from Texas and Ohio, with regard to adverse incidents, and then more time for committee questioning, and go on to the Canadian experience. Then we will have a focus and charge for the committee. We're going to have to wait until slightly after lunch before we're given our exact focus of what we're supposed to do, but I think most of us have a general idea. Beth Yetley will give us further detail on exactly what she wishes the committee to do, and we'll have an opportunity to clarify any questions that may arise with regard to our exact purpose and focus.

Then in the afternoon, we will have a report on safety evaluation and then another open public hearing, and after that, we will recess and reconvene again tomorrow morning to have more open public hearing and discussion, and then the committee will discuss and deliberate and come to some advisory information for the Food and Drug Administration.

Now, remember, this committee is an advisory committee and it is just that. We are asked from time to

time to provide advice to the Food and Drug Administration. Our deliberations are advisory in nature, not binding, simply to provide our best estimate with regard particularly to safety issues to the Food and Drug Administration.

I'd like to mention that after all our discussion is done on Wednesday, we will go around the room, and everybody at the table will have an opportunity to give a summary statement, if they so desire, concerning what they've heard in the meeting and their feelings with regard to the public safety aspects that are under consideration here.

I would like everybody that wishes to speak from the committee to be sure and identify yourself each time you address the microphone because this is being recorded, and without that, it's difficult to attribute comments in the record to whoever is speaking. So if you want to make sure that your comments are attributed to you, identify yourself each time you speak into the microphone.

I'd like to start by going around the table here and introducing everybody. We have a rather large group here today. The Committee on Food Safety, as I said, has been augmented by a number of subject matter experts, and I think that we will just go around the room. Give us your name, your organization, and we'll proceed around.

We'll start down in the far corner with Loren Israelson.

MR. ISRAELSON: Good morning. I'm Loren Israelson. I'm Executive Director of the Utah Natural Products Alliance based in Salt Lake City, which is a major center of dietary supplement manufacturers in the United States. I'm serving as an industry representative.

DR. RICAURTE: Good morning. My name is George Ricaurte. I'm in the Department of Neurology at Johns Hopkins University School of Medicine, and my background is in pharmacology.

DR. DENTALI: Good morning. My name is Steven Dentali. I'm with Dentali Associates. I'm a consultant to the natural products industry. My training is in pharmaceutical sciences, pharmacognosy, and herbal medicine.

DR. FONG: Hello. My name is Harry Fong, Professor of Pharmacognosy, College of Pharmacy, the University of Illinois at Chicago.

DR. HUI: Hi. My name is Ka Kit Hui of UCLA School of Medicine. I'm director of the Center for East-West Medicine. I'm an internist, I'm a clinical pharmacologist, and I'm also interested in herbal medicine and Chinese medicine.

DR. BRUNER: Good morning. My name is Dr. Denise

Bruner. I'm a private practitioner interested in bariatric medicine, which is weight reduction, and I'm also the Vice President of the American Society of Bariatric Physicians.

DR. CROOM: My name is Ed Croom, and I work on phyto medicines in the School of Pharmacy at the University of Mississippi and in the Department of Pharmacognosy.

DR. JASINSKI: My name is Don Jasinski. I'm Professor of Medicine at Johns Hopkins University School of Medicine, and chief of the Center for Chemical Dependence at Johns Hopkins University Bayview Medical Center. My area of expertise is clinical pharmacology and the measurement of abuse potential of drugs.

DR. BLACKBURN: Henry Blackburn, Division of Epidemiology, School of Public Health, University of Minnesota.

DR. APPLEBAUM: Rhona Applebaum, Executive Vice President for Scientific and Regulatory Affairs for the National Food Processors Association. My background is nutrition and food micro.

DR. BENEDICT: Steve Benedict, Department of Microbiology, University of Kansas.

DR. CHASSY: Bruce Chassy, Professor of Food Microbiology and head of the Department of Food Science and Human Nutrition at the University of Illinois.

DR. FUKAGAWA: Naomi Fukagawa, Department of Medicine, University of Vermont.

DR. ASKEW: And I'm Wayne Askew. I'm the director of the Division of Foods and Nutrition at the University of Utah, Salt Lake City, Utah, and I am sitting in for the normal chair of this committee, Dr. Ed Brandt. Dr. Brandt has been ill. He is recovering now and sends his best, but his doctors suggested that he should not travel right now, and so I'm filling in for Dr. Brandt.

DR. LARSEN: I'm Lynn Larsen. I'm from FDA and the Exec Sec of the Advisory Committee.

DR. HSIEH: I'm Dennis Hsieh, Professor of Environmental Toxicology, University of California-Davis.

DR. KATZ: I'm Robert Katz from the Department of Pediatrics, University of New Mexico School of Medicine.

MS. RICHARDSON: Donna Richardson, Howard University Medlantic Women's Health Initiative.

MR. GUZEWICH: Jack Guzewich, New York State Health Department Food Protection. I'm also on the epidemiology faculty at the School of Public Health, University at Albany.

DR. POTTER: Morris Potter, Centers for Disease Control.

DR. WANG: Mary Wang, food and drug scientist with

the California Department of Health Services.

DR. ZIMENT: I'm Irwin Ziment, medical director of Olive View, UCLA Medical Center in Los Angeles. My area of interest is asthma, with particular reference to the use of betaragonists(?).

DR. GEORGITIS: I'm John Georgitis. I'm at the Department of Pediatrics, full professor of pediatrics, Bowman Gray School of Medicine. I'm an allergist, immunologist, and pediatric pulmonologist.

DR. MARANGELL: I'm Dr. Lauren Marangell. I'm Director of Clinical Psychopharmacology at Baylor College of Medicine in Houston, Texas.

DR. INCHIOSA: I'm Mario Inchiosa. I'm Professor of Pharmacology at New York Medical College.

DR. WOOSLEY: I'm Dr. Raymond Woosley. I'm Professor and Chairman of the Department of Pharmacology at Georgetown University. I'm a clinical pharmacologist with a focus on cardiac arrhythmias and drug-induced cardiac toxicity.

MR. FORD: Michael Ford, Executive Director of the National Nutritional Foods Association. We represent about 4,000 members throughout the country, both health food stores and suppliers and manufacturers and distributors of health foods and dietary supplements.

MS. BINZER: I'm Peggy Binzer. I'm with the Office of Special Nutritionals, FDA.

MS. HARDY: I'm Connie Hardy with FDA, Office of Special Nutritionals.

DR. ASKEW: Okay. Thank you very much. There are some members of the committee that will be arriving later that aren't here right now, but we have, as you can see, quite an interdisciplinary group around the table here, and I think this brings a good diversity of professional opinions and focus on the safety matters that we're asked to consider. I thank everybody for being here this morning and for taking part in this deliberation.

Now I'd like to introduce our Executive Secretary of the Committee on Food Safety, Dr. Lynn Larsen, who has some administrative announcements.

DR. LARSEN: Dr. Askew has already made the first announcement about Dr. Brandt, and we do send our regards to him.

For those members at the table here who haven't yet found your break-time retreat, it is up on the second floor in the Executive Board Room.

I have several notes about participants, the schedule in your notebooks. The first note says that the affiliation of Dr. Ho, one of our guest speakers, was

printed incorrectly in the materials we distributed. Dr. Ho is the Chief, Product Regulation Division, Bureau of Non-Prescription Drugs, Health Protection Branch, Health Canada.

Dr. Crawford, who I don't see at the table yet, is a former member of this committee and, while he was a member of the committee, served on the working group that met last October. Therefore, we have invited him back to participate in this meeting as a guest at the table.

There has been a number of changes in the schedule from that announced in the Federal Register. The open public hearing was originally announced as being from about 3:00 to 5:00 today. We have now divided that and lengthened that. It is divided into three sections. I believe everyone who registered ahead of time has been informed about the section in which they are scheduled to speak. The three sections are beginning at about 9:30 this morning, at about 4:30 this afternoon, and about 8:30 tomorrow morning.

Under Tab C of your notebooks--we had someone call in and ask what happened to the second page of the press release. Well, the second page is there. What's missing is the last word of the first page, which should be the word "euphoria" and then a period. So if you can add that to your press release first page.

All of the participants here at the table have

been screened for conflict of interest with respect to a long series of companies and products that are affected by this hearing or might be affected by this hearing. I think we've now got--our guest speakers, at least, have signed the forms that we need them to sign with respect to conflict, and the staff will make sure that it gets done. Before you speak, please make sure you see the staff and sign those forms.

Amongst the rest of the committee, we only had two potential appearances of conflict, and I would like to mention what has happened with those. We have asked for and received waivers for Dr. Dentali and Dr. Askew.

Dr. Askew is the Director of the Division of Nutrition at the University of Utah. A graduate student in his division and under his professional supervision will conduct a clinical trial of a developmental product for Wyder(?) Nutritional Products. The product contains, among other ingredients, a botanical source of ephedrine alkaloids. A clinical research agreement is being negotiated at this time with Wyder for which the graduate student will be the principal investigator. The agreement will provide the graduate student with $10,000 in support for research expenses through the University of Utah Division of Nutrition account. Dr. Askew, as director of

that division, will administer the account for the university, but will receive no personal remuneration. A waiver for the potential conflict has been approved by FDA to permit Dr. Askew to participate in this meeting and to provide his expertise as a nutritionist.

Dr. Dentali has advised us that he served as an expert witness for the defense in an administrative hearing in the State of New York wherein the state sought action against the sale and distribution of specified products containing ephedrine. He also represented the Council for Responsible Nutrition at a U.S. pharmacopeia conference. I believe that was here in Washington a few weeks ago. He was a paid consultant at both of these events. He received a total of $8,000 for those consultant fees. At the present time, these consultancies have been completed, and there are no pending financial agreements between Dr. Dentali and these organizations. A waiver for the potential conflict has been approved by FDA to permit Dr. Dentali to participate in this meeting and to provide his expertise as a natural products chemist.

I think that concludes all of the announcements I need to make at this particular time.

DR. ASKEW: Thank you, Dr. Larsen.

At this time we will go into an introduction to

the issue and then a review of the deliberations of the working group. Now, remember, I said that the working group met in October 1995. The Committee on Food Safety is a relatively large committee and often has a working group consider the issue and then brings it before the entire body, and this is what occurred in October of 1995.

I'd like to introduce Dr. Elizabeth Yetley from the FDA at this point. Dr. Yetley will introduce us to the issue and give the committee some opportunity to ask any questions of clarification before a summary of the working group meeting is presented. Is Dr. Yetley here?

We will give Dr. Yetley a moment to get her slides together.

Dr. Larsen, do you have any comments with regard to the working group meeting that you could make at this time, or do you want to wait until after Dr. Yetley?

DR. LARSEN: I think I'll wait until after Dr. Yetley. Ms. Binzer and I sort of have a tag team going on her presentation and mine. My presentation is actually just a summary in place of the summary that Dr. Brandt, as Chair of that working group, would have made.

DR. ASKEW: I might mention in the public hearing we're going to have--one of the individuals who wanted to make a public comment has, as Dr. Larsen mentioned earlier,

a scheduling conflict, and so we're going to have a--is that right?

DR. LARSEN: Since I last talked to Dr. Askew yesterday afternoon, there have been a number of changes in the public hearing schedule.

DR. ASKEW: Why don't you give us an update?

DR. LARSEN: Okay. I'll give you an update while we're waiting.

We had one person who had originally said that because of employment conflicts and a court subpoena, she wasn't going to be able to attend tomorrow when I scheduled her. So we were going to sort of put her in at 1 o'clock this afternoon. When I got back to the office late yesterday, that subpoena had been canceled. She will speak tomorrow, so we can forget about that little item on the Chairman's agenda.

I have some notes here that Ms. Adele Audet from Massachusetts Department of Public Health will not be with us during the open public hearing, so we will cancel her out for this morning. This may get us a little faster through the morning.

And Mr. Bill Appler, I just had a note that he would prefer to speak tomorrow morning.

So those are the schedule changes that I have at

this point in time on the open public hearing.

Dr. Yetley is catching her breath at the end of the table.

DR. ASKEW: Dr. Yetley, we've just had the introductions and a general introduction to what we're going to do here today, and now we're ready for you to introduce us to the issue, if you're ready to go.

Your microphone is not on yet, I don't believe, Dr. Yetley.

[Pause.]

DR. YETLEY: Is it on now? Okay. Welcome to the Food Advisory Committee on the safety of ephedrine alkaloids as contained in dietary supplements.

I also don't have light. If somebody could come and help me turn the light on, I'll try to keep going in the dark here for a minute.

We had asked members of the working group that first met with us last October to evaluate our growing concerns at that time about the safety of ephedrine alkaloid-containing dietary supplements to join all of the members of the full Food Advisory Committee meeting for this session for the next two days.

There are several reasons for this meeting: first, to provide an update since the October meeting;

secondly, to brief the full Food Advisory Committee on the conclusions and recommendations of October's working group; and, lastly, and most importantly, to elicit final expert opinions on the best solutions for resolving the safety concerns associated with the use of these supplement products.

Let me just briefly provide a little bit of background, and then more detail will be provided throughout the next two days, as to why we are here and what our concerns are. To date, FDA has received over 600 reports of illness or injury, some of them clinically serious, associated with the use of dietary supplements containing ephedrine alkaloids. When we met last October, we had received just over 300 reports of adverse events. The number has since doubled.

Most of the adverse events reported occur in young to middle-aged women, often those who are using the products for purposes of energy or weight loss. However, adverse events have also been reported to occur in many, a broad spectrum of the population, including young adult men who are using these products for claimed usefulness in body building, and in one case a death because of so-called use of these products as an alternative to illicit street drugs.

The reported adverse events primarily involve the

cardiovascular system, including heart attack, stroke, and cardiac arrest, and the central nervous system, with symptoms and signs such as anxiety, insomnia, psychosis, and seizures. These effects are generally consistent with the known physiological and pharmacological effects of ephedrine alkaloids. These effects are seen in healthy individuals as well as those that have underlying factors for some of these conditions. Of great concern to the agency are the heart attacks and strokes and other serious, clinically serious injuries and illnesses that we're seeing in young adults who would not be expected to have risk factors for these conditions.

Now let me briefly explain the meeting agenda and the materials that you have received. A summary of the presentations made at the October 1995 working group meeting will be presented after I finish by Ms. Peggy Binzer. This will give you a quick overview of the issues that were discussed at that meeting. She will include in her summary the summaries of the chemistry of the ephedrine alkaloids in botanicals, as well as some information on traditional use.

More detailed information on these topic areas was included in the briefing books that were provided to the working group last October. We have as a resource to answer any additional questions on this Dr. Bill Obermeyer from the

Center for Food Safety and Applied Nutrition.

After Ms. Binzer, Dr. Lynn Larsen will summarize the conclusions reached last October by the working group. Minutes of that meeting were included in the briefing book that we mailed several weeks ago to you under Tab D.

Because of considerable state interest in the safety of ephedrine alkaloid-containing dietary supplements, we will begin the formal presentation this morning with Dr. Cynthia Culmo from the Texas Department of Health, who will discuss the adverse events that have been reported in the State of Texas and the ways in which Texas is addressing the public health concerns associated with these products at the state level. In addition, Dr. Frank Wickham from the Ohio State Board of Pharmacy will discuss the State of Ohio's concerns and activities with respect to these products.

We have also asked a representative of the Canadian Government to discuss their experiences with ephedrine alkaloid-containing products, particularly because a Canadian monograph was used by several members of last October's working group to support recommendations that they made during that meeting. Ms. Micheline Ho will make the presentation from the Government of Canada.

This afternoon's session will include the most detailed information on the components of FDA's evaluation

of the safety of ephedrine alkaloid-containing dietary supplements, and it's really broken into two parts: the market review and the safety review.

Information on FDA's review of the marketplace can be found in several locations. First, the products that we have purchased and included in our market review can be seen at the table over here on the side of the room. Last October's briefing book contained a summary of the information collected in the market review conducted in August and September of last year. At that time, FDA collected about a hundred products to get an idea about the types of products in the marketplace and the level of ephedrine alkaloids they contained.

This survey was updated this year following the death of a young man on a so-called street drug alternative that contained a botanical source of ephedrine alkaloids. Results of this update combined with the earlier survey were in the briefing book that was mailed a couple of weeks ago, which contained combined information from both surveys. Additionally, you received some graphic materials by fax this week. The more detailed presentation will be made by Ms. Connie Hardy this afternoon.

Following Connie's presentation on the market review, Dr. Lori Love will present a discussion of the basis

for our concerns about the safety of ephedrine alkaloid-containing dietary supplements. Again, information on the safety concerns and data can be found in several places. Both the briefing book from last fall as well as the updated briefing book sent out recently contain a safety review section. Last fall's book contained considerable information on the known clinical and pharmacological effects of ephedrine alkaloids, as well as information on the adverse events received up to that point in time.

The newer briefing book and materials faxed to you last week contain an update on the adverse event reports that we received since the October meeting. Also, as we did at the working group meeting, we've provided access to redacted medical records and other information related to the adverse event reports through the public docket, so the information is available to any interested party. We have also brought a copy of these records to this meeting in case any members of the committee wish to review them more closely during the meeting.

As always, we will have open public hearings so that any interested parties who wish to present their perspectives are free to do so. We have divided these into several time frames: one this morning, one at the end of today's discussion, and one tomorrow morning.

Just one last agenda item. I will present a brief overview of the focus, charge, and questions to the committee just before the discussions of the market and safety reviews this afternoon by Ms. Hardy and Dr. Love. The purpose of presenting them very briefly to you before those detailed presentations is to sensitize the committee as to what is expected of them so that you can target your attention and focus your questions on those issues that are most relevant to the purpose of this meeting. We will then discuss these in more detail tomorrow morning to make sure that you are clear as to what we are asking you to do so that we can answer any questions you may have before you start your in-depth detailed discussion.

Now let me briefly comment on the types of expertise that we've selected originally for the working group and that we have made sure that we have covered at this meeting. There were a few members of the working group, last October's working group, that were unable to attend this meeting, and we have tried to replace them with expertise that is similar to that which the original members had.

We carefully selected the makeup of our working group to draw upon the expertise and experience of all of the relevant scientific areas that we felt that we needed

information from. The selected expertise was driven by the nature of the substance, a botanical or a natural product, and the nature and pattern of the reported adverse events. Thus, we asked for experts in cardiology since a large number of our adverse events were cardiovascular in nature. We also have experts in neurology and psychiatry because of the central nervous system effects and the psychoses that were seen. Experts in pharmacology can provide information on the metabolism and toxicology of the ephedrine alkaloids. We have experts in pharmacognosy to evaluate the botanical substances and provide their knowledge of the botanicals, both chemically and from the perspective of their traditional uses.

We have also included nutrition and obesity experts because many of these products are taken in conjunction with very rapid weight loss, and we thought that we needed to be able to sort through the weight loss versus the substance effects.

Finally, we have asked the industry and consumer representatives to bring to the table their knowledge of the marketplace and their viewpoints of the respective groups that they represent. We feel that the full committee will be very helpful in reviewing and in listening to what the working group has heard and in helping the working group to

reach some final conclusions and recommendations.

We recognize that the task of the committee is difficult, but we have confidence that we have the necessary expertise and experience here to come up with useful recommendations.

Now, before I finish, let me briefly give you some background information on the Dietary Supplement Health and Education Act so that you understand what a dietary supplement is. This act defines a dietary supplement as a product that contains one or more of the following ingredients: a vitamin, a mineral, an herb or other botanical, amino acid, or any other dietary substance for use by man to supplement the diet by increasing total dietary intake. And it can be a concentrate metabolite, constituent extract, or a combination. So it is a very broad range of products. The act also defines the form in which the dietary supplement is to be presented, and it is not to be represented as conventional food. It must be labeled as a dietary supplement.

The products that are subject to the Dietary Supplement Health and Education Act must meet one of the safety standards that are listed here. The one that is most commonly quoted is: A product is adulterated if it presents a significant or unreasonable risk under labeled conditions

of use. In addition, dietary ingredients are exempt from the food additive provisions of the Federal Food, Drug, and Cosmetic Act. This means that these ingredients do not have to undergo review or approval by FDA prior to marketing.

While manufacturers and distributors are responsible for ensuring that their products are safe, they are not required to perform clinical or other studies to establish the safety of their products prior to marketing.

If I could have the slides off, please?

Let me also just briefly mention what this meeting is not about. This meeting is not about whether dietary supplements containing ephedrine alkaloids should be regulated as drugs instead of as dietary supplements. That is a given with the act. It is also not about whether you believe there is documented evidence or there is not documented evidence for their effectiveness. They are available in the marketplace.

The focus of this discussion is the scientific base and the scientific input that we need to understand and take account of as we deal with the safety concerns that we have relative to the availability and use of these products in the marketplace.

With these ground rules in mind, I look forward to hearing your discussion. Thank you.

DR. ASKEW: Thank you, Dr. Yetley.

At this point in time--Dr. Yetley has promised to give us our full charge later on this afternoon, but does anyone from the committee have any questions of Dr. Yetley before we proceed into the review of the working group deliberations? Anyone at all?

[No response.]

DR. ASKEW: If not, then we'll go ahead and proceed. Next on the list is Dr. Larsen, who is going to make some comments with regard to the 1995 working group meeting.

DR. LARSEN: The working group was assembled to assist FDA in addressing the concerns, as Dr. Yetley has said, about adverse events associated with a variety of dietary supplements and similar products containing ma huang and other related botanicals that have ephedrine alkaloids as natural chemical constituents. In some cases, the supplement product contained extracts or concentrates of the herb, and you've heard Dr. Yetley's comments.

The minutes of the meeting are contained in your notebooks. Following presentations by FDA, the public, the industry, and other interested parties, the working group was asked to respond to a series of questions. Those questions are attached to the minutes of last fall's meeting

as well.

The questions addressed the association of the adverse events with the products, the quality of the data relating the association, the seriousness of the events, and the conditions of safe use, if any, that might be delineated for the products. The working group was not asked to address the legal status of the products--i.e., whether the products were foods or drugs--or the effectiveness of the products for any labeled function. That is a repeat, again, of what Dr. Yetley just said.

Now, Ms. Peggy Binzer, Ms. Margaret Binzer--we call her Peggy--will provide a summary of the data that was considered by the working group, and after her presentation, I will briefly summarize the conclusions of that working group meeting.

MS. BINZER: Good morning. I have a few slides.

I have been asked to provide a brief overview of the information FDA provided to the working group last October. I'll begin with a review of the botanical sources of ephedrine alkaloids and their relevance to traditional uses in medicine. Then I'll summarize the information obtained in FDA's first market review of products containing ephedrine alkaloids. Finally, I'll briefly highlight information available last October about the adverse event

reports associated with the use of these products. Dr. Love will give a more complete review and update of this information later this afternoon.

The ephedrine alkaloids are natural chemical stimulants found in several botanical products. Ma huang is the Chinese name for the aboveground parts of four plant species belonging to the genus ephedra. These and a number of other ephedra species produce optically active alkaloids in total concentrations ranging from 0.018 to 3.4 percent.

The natural alkaloids are ephedrine, pseudo-ephedrine, methyl ephedrine, methyl pseudoephedrine, norephedrine, and norpseudoephedrine. The ephedrine alkaloids have amphetamine-like structures.

Although the relative proportion and absolute levels of the various ephedrine alkaloids vary among species, in most species ephedrine is quantitatively the most predominant alkaloid with lesser amounts of pseudoephedrine and other alkaloids present. As an aside, there are other species that have been reported to contain ephedrine, such as Sida cordifolia.

Ma huang has a long history of use in traditional Chinese medicine for the treatment of the symptoms of colds and to relieve respiratory symptoms. The botanical was typically consumed as an herbal infusion, that is, a tea,

either alone or mixed with other herbal ingredients. Commonly used dosages of the raw botanical in traditional medicine generally averaged five to six grams, which contains about 15 to 40 mg of ephedrine.

To better understand the marketplace, FDA conducted its first market review of products containing ephedrine alkaloids. As a practical matter, the review was a snapshot of national products available predominantly on the east coast, as well as through telephone orders. The market review included approximately a hundred products marketed in a variety of forms, such as capsules, tablets, liquid drops, liquid sprays, powders, teas, and liquid drinks.

The review consisted of two phases. First, we reviewed product labels to identify the ingredients contained in the products and the conditions of use, including directions for use and warning or cautionary statements. In the second phase, FDA laboratories analyzed a single sample of each of these products for the ephedrine alkaloids. Because of possible interactive effects between ephedrine alkaloids and xanthine alkaloids, we also analyzed the products for their xanthine alkaloid content, specifically for caffeine, theobromine, and theophylline.

We conducted the market review not for the purpose

of looking at one product versus another, but rather to gain a big picture of the marketplace, of the products available, the range of conditions of use, and the variety of warning or cautionary statements for these products.

Let's consider what we found in the review. With respect to ingredients, some products only contained ma huang or an ephedra extract. Other products contained ephedra or its extract combined with other botanical ingredients, including cola nut or other caffeine sources, vitamins, minerals, amino acids, and other ingredients. Many of the dietary supplements contained more than 10 different ingredients, some with known or suspected physiological and pharmacological activity.

The collection of products in the market review were promoted for a variety of uses, including energy, weight loss, body building, and ergogenics, and that is performance enhancement. The products contained a variety of directions of use.

With respect to warning or cautionary statements found on the labels of products, approximately 15 percent of all the dietary supplements collected in the review did not bear warning statements of any kind; 85 percent of the dietary supplements bore warning statements ranging from very general statements such as, Consult your physician

before beginning any nutritional or exercise program, to more specific warning statements. The more specific warning statements tended to have elements relating to recommendations not to use the product if a person suffers from certain medical conditions or diseases, experience certain adverse effects, is taking certain medications, or is under a certain age.

Turning now to the results of the analysis, the results indicated that of the hundred products in the market review, almost 50 percent had total ephedrine alkaloid levels above or equal to 20 mg per serving. The level of total ephedrine alkaloids contained in the products ranged from below detectable limits to 110 mg per serving.

Approximately 65 percent of the products contained ephedrine alkaloids in combination with xanthine alkaloids. The xanthine alkaloid content of the products ranged from below detectable limits to 346 mg per serving. In products containing both ephedrine and xanthine alkaloids, there was no consistent pattern of concentration as shown in this scatter plot, with ephedrine on the horizontal axis and xanthin on the vertical axis. Oh, it's upside down. Sorry about that.

At the time of the working group meeting, FDA had received more than 330 reports of adverse events, many of

them serious, in individuals consuming dietary supplements with sources of ephedrine alkaloids. The majority of the serious adverse events associated with the use of the products primarily fell into two categories, and as Dr. Yetley outlined, the first is cardiovascular effects, including cardiac arrest, heart attack, and stroke. The second is central nervous system effects, including anxiety, insomnia, psychosis, and seizures.

An evaluation of the adverse event reports revealed similar patterns in the nature and severity of the illnesses and injuries in individuals using many different dietary supplement products containing ephedrine alkaloids. The adverse events are associated with a broad spectrum of the population and included individuals with underlying factors that may have influenced the frequency, pattern, or severity of the adverse events. However, the effects were reported in otherwise healthy individuals, often young adults, with no history of complicating factors and who were taking ephedrine alkaloid-containing dietary supplements according to the directions of use on the product.

Many events indicate individual sensitivity to the effects of sympathetic stimulation. Many reports occurred following very short-term use of the products. In short, the adverse event reports indicated that otherwise healthy

individuals may experience serious illnesses or injuries when they consume dietary supplements contained ephedrine alkaloids at levels currently in the marketplace.

The nature and pattern of the adverse events are consistent with the known physiological effects of sympathomimetic agents, that is, agents mimicking the effects of the sympathetic nervous system, as well as with case reports from the scientific literature, adverse events occurring in controlled clinical trials, and adverse events reported from the use of OTC drugs.

This has been a brief summary, but I hope that it gives you some background and a context for the rest of the meeting. I'd be happy to answer any questions you may have, and with me today is Dr. Bill Obermeyer, who is an FDA chemist, who has been responsible for most of the chemistry discussed in this presentation.

Thank you.

DR. ASKEW: Yes, Dr. Jasinski?

DR. JASINSKI: I just have a question. Some of the products are extracts that are sold, and some are put into capsules?

MS. BINZER: Yes. The products range. Many of them are concentrated extracts, and this was found on the labels of the products. And then the majority actually do

contain concentrated extracts and also the majority do contain other ingredients as well.

DR. JASINSKI: I have a typical question. Ephedrine has been sold as an OTC drug in this country for over 50 years. If I understand this, does this mean that if I go out and prepare ephedrine that's OTC I'm saying, no, I'm going to switch this so this is a dietary supplement, I can do this and exempt myself from any of the regulation of the OTC drugs? Who decides whether--I mean, if you make an extract, it becomes a drug. When does an OTC drug become listed as a dietary supplement and who decides that?

MS. BINZER: The extracts are extracts from the botanical product where OTC drugs typically are synthetic sources of--in the case of OTC bronchodilators, they are ephedrine alone, where the products that we're finding on the market are extracts from the botanicals. So they not only contain ephedrine, but they also contained a variety of other alkaloids, including pseudoephedrine, norephedrine, methyl ephedrine.

DR. YETLEY: Maybe I can just add to that a little bit? And we also have general counsel here, if we need. It's really the intended use of the manufacturer as to whether it's a food or a drug, and if they want to market it as a dietary supplement, it has to be labeled as a dietary

supplement. If it's intended for therapeutic uses that are associated with the OTC drugs and have had monographs or have had status as an OTC drug, then it would be the manufacturer's choice to meet the drug standards in marketing them that way. But if they're marketed as a food, they have to have a food label as a dietary supplement.

DR. JASINSKI: But I could see gray areas where people--I mean, what we're really talking about is a gray area, and who makes that decision? What you're saying is that the decision is made by the manufacturer, not the FDA.

DR. YETLEY: Well, it's the interpretation of the manufacturer's intended use.

MS. NICKERSON: My name is Louisa Nickerson. I'm a lawyer--

DR. LARSEN: Please come up to the microphone. Coming to the microphone is Louisa Nickerson from our FDA Office of General Counsel.

MS. NICKERSON: What Dr. Yetley said was correct. I just wanted to add a couple things.

First of all, in order to qualify as an OTC drug, a product has to comply with the OTC monograph, including labeling. And--what was I going to say? Yes, I guess that was the only--oh, the other thing I wanted to say was there's nothing to stop a dietary supplement manufacturer

from using ephedrine, the pharmaceutical form, as opposed to ephedra in a dietary supplement if the product is labeled as a dietary supplement and meets the other requirements of the act for dietary supplements.

DR. ASKEW: Yes, Dr. Ziment?

DR. ZIMENT: What I find difficult to understand is: What is the difference between a prime effect and a side effect? If people are taking ephedra to be alert or to be stimulated, how can insomnia be determined as being a side effect?

DR. YETLEY: I think that what we're looking for--a couple points here. Number one, we're looking for effects that would cause safety concerns when they're used as foods and not used for therapeutic purposes. Foods would be used for non-therapeutic purposes.

DR. ZIMENT: Yes, but I don't think that really answers the question of how one can say how many reports there are of side effects without perhaps analyzing those side effects and saying which are serious and meaningful and those which are not really meaningful.

DR. YETLEY: Let me suggest that we need to go through the fuller discussion and the fuller presentations, and then if this is still a point that's confusing, bring it back up before you start your discussion.

DR. ASKEW: Yes, Dr. Israelson?

DR. ISRAELSON: Yes, I just wanted to comment. I was concerned by what Ms. Nickerson said that the addition of ephedrine to a dietary supplement is permissible, and I don't believe that that's how we read the DSHEA, that the addition of any Category 1 OTC drug ingredient would adulterate dietary supplements. This would be true for anything in addition to ephedrine, so I'm concerned that the committee not believe that one can cavalierly put a drug ingredient into a dietary supplement and this would be regarded as acceptable.

DR. ASKEW: Could someone clarify that point? I think it's an important point, whether the ephedrine alkaloids contained in a dietary supplement must be of botanical origin or whether they can be of chemical origin and added.

Dr. Dentali?

DR. DENTALI: Correct me if I'm wrong, but my understanding is that ephedrine is purified, is not a dietary supplement, it's not an herb or an herb extract. Maybe we'd have to go to how it's created, but my understanding is that purified ephedrine is not considered an herb or an herb extract so, therefore, is not a dietary supplement.

MR. ISRAELSON: To add to that, if I may, Mr. Chairman?

DR. ASKEW: Yes.

MR. ISRAELSON: Under the statute, ephedrine or other drug ingredients would have to be an old dietary ingredient to qualify to be sold as a dietary supplement. I don't believe that would be the case, certainly with ephedrine hydrochloride or other typical drug ingredients of that nature. And as Dr. Yetley pointed out, there are requirements if you want to sell something as a new dietary ingredient. So, historically, I'm unaware of the use of ephedrine hydrochloride as a synthetic element as a dietary supplement.

DR. ASKEW: Dr. Yetley, would you like to clarify this? The legal counsel and you have kind of caused a little bit of uncertainty right now.

DR. YETLEY: There's a big gray in here, as someone said. I don't know. I think general counsel may need to help me out. I think that there is some ambiguity as to what qualifies and what doesn't qualify as a dietary ingredient. And there are certain specific statements in the definition of the dietary ingredient, and there's also that catch-all statement about any other substance necessary or desired to increase dietary supplement intakes.

I'm not sure that this particular question is that germane to the safety issues. What we're really trying to find out is: Are the products, as they are marketed as dietary supplements, are the products as marketed as dietary supplements, do they create safety concerns? What are those concerns? And how do we address them?

DR. ASKEW: Yes, thank you. We don't want to get led astray here. If you find further information on this and want to comment further on it this afternoon, why, you certainly could, Dr. Yetley.

We're ready for Dr. Larsen's comments.

DR. LARSEN: I might also suggest that you might want to let FDA make the decision as to whether the addition is--you know, the interpretation under the act, whether that addition is--the focus of this meeting is really on the herbal extracts and the herb products. Am I correct, Dr. Yetley?

DR. YETLEY: The issue is on products marketed as dietary supplements which contain ephedrine alkaloids.

DR. LARSEN: Okay. You all have the minutes in your notebooks. The summary that follows reflects the general view and overall conclusions of the working group as a body. It does not reflect every view expressed by members, especially for the more debated issues. Again, I

would refer you to those minutes for additional details. If you want real detail, you might look at the transcript of the meeting itself if you want to spend a long, sleepless night--or maybe get to sleep at night.

I am sure that the working group members who are here at the table will again express their particular points of view during this committee discussion today and tomorrow.

There was debate about what conclusions could be drawn from the data from the adverse event reporting system and the extent of those conclusions. With appropriate adjustments to considering the shortcomings of adverse event reporting systems and all the available data, including that from pharmacologic literature, the working group found that there was sufficient information to conclude that there may be an association between consumption of the products and the reported serious adverse events.

FDA used a list of criteria to evaluate the association between those serious adverse events and consumption of products containing ephedrine alkaloids. The working group agreed that there was a relationship between reported illnesses or injuries and the factors that were evaluated. However, there was debate on whether the observed data patterns could be described as consistent or as similar. In other words, there was some debate about

what word was to be used to describe those patterns.

The working group agreed that safe conditions of use in foods and dietary supplements could and should be described for botanical products containing ephedrine alkaloids. The conditions include dose, that is, per serving limits, limits on the dose or the per serving use, and daily use limits; directions for use; warning and cautionary statements; and appropriate good manufacturing practice requirements.

Dose or serving limits were a point of considerable debate. One that the working group referred to as the Tyler-Croom proposal is specifically noted in the minutes. Lower levels were also suggested. However, the working group agreed that the ephedrine alkaloid limit should be below that for currently marketed OTC drugs, and label instructions should advise consumers that more frequent use or using more than instructed does not increase effectiveness.

The working group could not reach consensus on safety of multiple component products, that is, products that contain botanical sources of both ephedrine alkaloids and other substances that might interact, such as botanical sources of caffeine. The working group strongly supported standards of manufacture and additional research on the

safety of these botanical products. And the working group agreed that labeling of products should contain a number of elements, including instructions for safe use and warning or cautionary statements.

Those are pretty succinct, I think, comments on a long discussion on what the working group debated. But that's my summary on behalf of Dr. Brandt of the working group minutes.

DR. ASKEW: If I might, Dr. Larsen, a summary of the summary would be then that the working group did find that there was enough evidence to suggest that the adverse effects were associated with the use of ephedrine alkaloids, and then some discussion as to a possible safe level was discussed, the safe level being somewhere under the current level for over-the-counter drugs containing ephedrine alkaloids, and then a final statement that a warning label should appear on these products.

Is that a fair summary of your summary?

DR. LARSEN: I think so.

DR. ASKEW: Okay. Now we're ready for comment. Does anyone here want to comment, particularly those that were at the working group meeting that want to add to that or those that were not at the working group meeting and want to further clarify what the working group discussed? It's

open for discussion at this point. Anyone at all?

[No response.]

DR. ASKEW: Okay. I think maybe at this point in time, though, for my clarification, if someone could provide what the current level, safe level, or the current level as specified for the over-the-counter drugs containing ephedrine alkaloids is for the benefit of the group here. Can anyone give us that figure?

DR. YETLEY: Well, there are several different products. There are some with ephedrine, there are some with pseudoephedrine, and there's some with PPA. We have a table on that. We could probably bring that in this afternoon if that would help.

DR. ASKEW: Okay.

Jack Guzewich?

MR. GUZEWICH: Yes, Dr. Askew, I believe that some of the OTC drug approvals, there has been an advisory committee that suggested that those be withdrawn. Is there rulemaking going on about removing some of the OTC drug uses for ephedrine?

DR. YETLEY: Do we have Mike Weintraub here? Or Debbie? We have Dr. Debbie Bowen from the OTC Drug staff that could answer that question.

MS. BOWEN: We do have an ongoing rulemaking. As

you know, we published a proposal in 1995 to remove ephedrine-containing products for bronchodilator use from the marketplace due to three events, one being diversion and difficulty containing that by the DEA under their current rulemakings, and also some evidence in our adverse event reporting system of misuse of the products, which we have further actually looked into, and, as well, an Advisory Committee meeting was held where these issues were brought to the Advisory Committee meeting, and it was a joint advisory drugs, Pulmonary and Non-Prescription Drug Products Advisory Committee, in 1994.

At that point, there were some suggestions made that perhaps the use of the product as a bronchodilator did not overcome these new sort of threats to the consumer, and we opened a rulemaking, proposed a rule, and we've received a number of comments back about that rule. They vary all the way from continuing to allow the use of the product as a bronchodilator--and I would say that's ephedrine at 12.5 to 25 mg; that was a question that came up earlier, at least for ephedrine--to removing the products from the marketplace. And we've received a number of comments back to that, including the Texas database form that's used for some of the OTC products, and we're undergoing that rulemaking right now, reviewing all of our adverse events

and, again, looking at what DEA has now done to try to contain the diversion of the OTC drug product.

We haven't come to a final decision about that yet.

Mr. GUZEWICH: A follow-up question. Are those drugs administered by tablet or by bronchodilator inhalers or both?

MS. BOWEN: Not by inhalers. It's tablet only.

DR. BRUNER: And is it 12.5, you said, to 25 mg? Is that daily or unit dose?

MS. BOWEN: No, that's the unit dose, not to exceed 150 mg a day.

DR. CROOM: A follow-up on that. You're saying that's the debate, but the current levels of dosage that have been official for the last number of years, would you comment on what those have been for the historical time period, not what's being debated at this time?

MS. BOWEN: Okay. Those doses are actually not being debated at this time. What's being debated is the continued availability of the product for the reasons that I outlined to you before; 12.5 to 25 mg for a long period of time.

DR. ASKEW: Dr. Jasinski?

DR. JASINSKI: Just one question. Has there been

consideration of controlling ephedrine under the Controlled Substances Act? Most of the concern of the DEA is not with ephedrine at a retail level. There's been huge amounts of ephedrine being diverted as a precursor for methamphetamine. So this has been at a chemical plant at a distribution level.

With regard to this, though, has there been--with regard to your misuse, is there sufficient evidence or do you have a case to recommend to the Secretary of HHS that this be controlled under the Controlled Substances Act? And is there sufficient public health evidence in DAWN(?) and things such as this?

MS. BOWEN: I think that you're going to have to ask someone else about the DEA aspects of this. Perhaps--

DR. JASINSKI: No, no, this is not DEA. The Department of Health and Human Services has the responsibility to make this recommendation under the findings, to make the recommendation to the Secretary of HHS, which has a statutory responsibility. But you're considering taking it off the market, and one of these could be with controlling it under the Controlled Substances Act. Is there enough public health and social harm to recommend control under the Controlled Substances Act? I know you're taking this--considering this action.

MS. BOWEN: We have considered the action. We've discussed it internally. I don't think there has been a definite opinion about what to do yet, unless somebody from GC(?) here or from CDER can talk about that.

DR. ASKEW: Dr. Fong?

DR. FONG: I have sort of a--a little bit off, slightly off, but a corollary question. Currently, pseudoephedrine and phenylpropanolamine are used in OTC. So what would happen if ephedrine is banned from the OTC market? Would pseudoephedrine and phenylpropanolamine follow up in also being removed from the market? They are, after all, similar alkaloids, and they are also derived from ephedra.

DR. YETLEY: I think that what we're really focusing on today is not the drug issues, but the dietary supplement issues. And I think that, again, if this becomes relevant to your discussion, we can bring it up tomorrow. But I think you need to hear some of the presentations first to understand some of the characteristics of the dietary supplements, and you may then find that they're quite different than the drugs. So if that question still is important to you after you've heard the presentations, bring it up later.

DR. FONG: It was just a curiosity on my part,

what the FDA's looking at in the future.

DR. YETLEY: Maybe you could talk this over with Dr. Bowen during the break.

DR. FONG: Thank you.

DR. ASKEW: Yes, Mr. Ford?

MR. FORD: I just have a process question. When this working group was empaneled last October, it culminated a series of very good communications between the industry and the FDA on the specific issue, and I think the agency did a great job of pulling together a diverse group of experts that could look at this problem from a variety of standpoints, which I thought was the charge because of the somewhat urgent nature of the problem. And I think that we expressed our concerns as an industry that we were not getting, as the agency doesn't, quick enough reporting on these adverse reactions, which enables--rather, prevents us from getting the information out to the makers of the products. When there's a problem, I think the makers want to know about it.

I guess my question is, that group was empaneled 10 months ago, and a lot has happened in the 10 months subsequent. And I'm wondering what has been the delay, because I think we were called here on an urgent sort of mission 10 months ago.

DR. ASKEW: Dr. Larsen will address Mr. Ford's question.

[Laughter.]

DR. LARSEN: Let's put it this way: I will attempt to address the question. I'm sure Beth will keep me on the straight and narrow on this one.

It hasn't been a lack of inaction by FDA in the meantime. The FDA and staff have been working with the recommendations that the working group said, considering and refining what those recommendations have been.

You have to remember that this committee operates under the requirements of the Federal Advisory Committee Act, and a working group is a subcommittee, and a subcommittee cannot act independently of that committee. The working group recommendations were originally scheduled for consideration in November. That was a scheduled one-day meeting of the full committee, which was following a two-and-a-half-day lengthy committee of another working group, and the issue at hand at that particular time took the entire attention of the committee, and we simply ran out of time.

We rescheduled the full Advisory Committee meeting to take up this issue, to get it off the committee's table, in February. For various reasons, that meeting ended up

having to be postponed by FDA. We subsequently sought at that time--we wanted to get this thing moving. We subsequently sought to poll the committee by mail to see if they would simply read the minutes, read the transcript, read the materials we provided, and approve the working group or comment on the working group minutes, and then--and this is a legitimate process under FACA--then pass that on officially to FDA.

There were a number of the members of the committee who felt they wanted full discussion and face-to-face discussion, and this, unfortunately, is the first time we've been able to pull the committee together, along with all the other expertise that we needed, to get that on the table for the full committee. And as you said, there has been a lot of activity in the meantime, a lot of water under the bridge, if you will. So as time progressed, we at FDA realized that we were going to have to have more than just simply a simple consideration of the working group minutes. There was additional information. There was additional adverse event reporting. And so that's what brings us to this meeting today.

DR. ASKEW: And there's your answer.

We're now going to proceed, unless there's a burning question, to the public hearing portion this

morning. We have 30 minutes scheduled here, and I'm going to turn the microphone over to Dr. Larsen to introduce the public comments.

DR. LARSEN: With the changes in the public schedule that have been happening on the fly here, we may have a shorter public hearing session this morning than I had originally planned. So the morning session may get accelerated and then some of the folks will be--the afternoon and tomorrow morning may be a little more lengthy.

Before I begin that, I have a couple of announcements that have been handed to me. Somebody has lost their parking receipts, and our staff members have those parking receipts. So if you have a parking receipt that you dropped on the floor somewhere, please check with our staff member, Ms. Sylvia Washington.

If Drs. Fong, Hui, and Ziment could see the staff at the break time, there is some paperwork you need to finish signing as well. I thought we had that all signed, but we do need to have you sign one more time.

We had a couple of folks interested in participating in the open public hearing, and they in the end could not attend this meeting. I also have one person who raised a question, indicated, at least tangentially, an interest in the open public hearing which I have scheduled,

and I have not yet heard if he is here. So we'll continue to carry him until the end of the meeting. We'll see if he does appear.

The first person who had expressed interest that we want to mention this morning is Ms. Pamela Richardson, a consumer from Ohio. She is not able to be here. You have in your packets a letter that she provided. Ms. Richardson is from Plain City, Ohio, and in her comments, if I can take the liberty of trying to summarize them in a sentence or two, she comments on the facts surrounding her son's death that has been associated with the use of an ephedrine alkaloid-containing product, and she also comments on her efforts to have those products removed from over-the-counter status.

I received at the very end of the day yesterday another letter from a Mr. Gonzalez and a Mr. Valori who represent a Mr. Nanney in Florida, and there's also a letter from Mr. Nanney. Now, you do not have those letters in your packet at this time. I handed it to the staff this morning first thing, and we should have them duplicated, if not by the end of the day, at least by tomorrow morning, for you.

The essence of those letters are that the first two gentlemen represent Mr. Nanney, as lawyers represent Mr. Nanney, a 29-year-old who suffered a stroke that they

attribute to a product containing ma huang. Mr. Nanney describes the circumstances under which he suffered that stroke, and as I said, you will get the details that they provide in those letters when you receive those letters.

That brings me then to the first scheduled speaker of this session, who is still scheduled for this session, Mr. Mike McGuffin, President of the American Herbal Products Association in Bethesda, Maryland. As each speaker comes to the microphone, if you would again repeat your name, your affiliation, and, if it's not obvious from your affiliation, what kind of support you had for coming to this meeting. I have provided each speaker with about seven-and-a-half minutes of speaking time. We'll see how strictly we have to restrict them to that as the time goes on. But at this point, seven-and-a-half minutes of speaking time for each speaker.

MR. McGUFFIN: Good morning. I'm Michael McGuffin. I'm the President of the American Herbal Products Association, or AHPA. AHPA is the national trade association consisting of approximately 200 members who manufacture, distribute, and import culinary herbs, and primarily herbal dietary supplements. As a responsible trade association, AHPA has a successful history over the last 12 years of achieving tangible results in the areas of

self-regulation and the establishment of standards relevant to herbal products.

I'm addressing you today with a joint position developed by AHPA along with the Council for Responsible Nutrition, which represents 80 manufacturers of dietary supplements and other nutritional products, the National Nutritional Foods Association, or NNFA, with its 4,000 manufacturer and retailer members, and the Utah Natural Products Alliance, a trade group made up primarily of dietary supplements manufacturers based in Utah.

Recommendations for including a cautionary label statement on all products containing any amount of ephedrine alkaloids were publicized by AHPA and NNFA in early 1994, two-and-one-half years ago. Industry recommendations to limit dosage of ephedrine alkaloids to conservative safe levels have been in existence since October of 1994. Recommendations to identify ephedra by its standard and common name and to assure the absence of all synthetic alkaloids were communicated to our members in January of 1995.

I was in attendance at the October 11, 1995, meeting of the Special Working Group of the Food Advisory Committee on foods containing ephedrine alkaloid to communicate to the group the details of the above

recommendations. I urged the committee at that time to recommend to FDA that such labeling dosage limitations and identification become matters of policy.

Since that October 1995 meeting of the Special Working Group, considerable attention has been given to products containing ephedra which are marketed as substitutes for illegal street drugs. The organizations which I represent here today are united in our belief that this class of products should not be considered to be legitimate dietary supplements.

We believe that the marketing of these products is illegal under the Controlled Substances Analog Enforcement Act of 1986, which forbids the sale of products which are represented as substitutes for illegal drugs and which is enforced by the Drug Enforcement Administration. We further believe that such products, if promoted in a manner which encourages abuse, may present a significant or unreasonable risk of illness or injury. The Dietary Supplement Health and Education Act of 1994 specifically provides FDA with the authority to act against products which present such risks, and we strongly encourage the agency to act within the framework of this authority.

I'd like to take a moment to reiterate some of the points made by Dr. Larsen regarding the conclusions drawn by

the Special Working Group during their meeting last October. These conclusions included agreements that the use of ephedrine alkaloids is not unsafe under all conditions of use; that dosage limits should be considered at some level below that historically used in OTC drugs, which is, as was clarified earlier, for ephedrine 12.5 to 25 mg per dose and 150 mg per day; with pseudoephedrine, I believe the doses are 60 mg per dose and 240 per day. I believe that the first numbers are much more relevant. We are looking at products that have a higher concentration of ephedrine than pseudoephedrine, which is the alkaloid mix as it exists in nature tends to have a lot more of the ephedrine in most of the species in commerce.

A further recommendation or agreement of this Special Working Group was that all dietary supplements containing ephedrine alkaloids must be labeled with cautions against use by persons under the age of 18, by pregnant women, by persons with certain diseases or psychiatric disorders, or by persons taking certain prescription drugs; also that the form of ephedra used in foods and dietary supplements must be the botanical, or a suitable derivative thereof--that is, not the synthetic; and that the alkaloid levels need to be evaluated for all products and stated on the labels of all products. Each of these conclusions are

consistent with positions taken by industry over the last two-and-a-half years.

The trade associations which I represent here today have shown by their actions and communications that they are willing to work with FDA on this issue. The conclusions drawn by the working group from their meeting last October are not significantly different from those which we have been advocating for the last several years.

It is our intention to continue to contribute to the efforts of this committee and, we expect, to support its conclusions. We believe that the kinds of recommendations which the working group discussed, if accepted by FDA, will be effective in addressing the safety issues relating to legitimate ephedra-containing products. Universal compliance can only be achieved through FDA action and a clear and detailed recommendation of this committee.

Thank you very much.

DR. LARSEN: Thank you. We've got a minute or two, if the committee has any questions. Dr. Ricaurte?

DR. RICAURTE: I had one quick question. How do the companies that you represent plan on dealing with the issue of potential misuse of the product? The two groups of people, individuals seeking energy or other individuals seeking weight loss, either of those ends clearly can be

associated with misuse of the compound or the product. And I guess my question would be: If an individual has unlimited access to your product, how does your group plan to ensure the safe use of these compounds?

MR. McGUFFIN: The only mechanism that I'm aware of that I believe that we can utilize and which I believe is effective is to label the products in a meaningful manner, to make sure that the consumers understand the risks associated with any abuse. We are not going to control individuals' consumption. We can inform them of what the consumption needs to be and inform them of the associated concerns related to over-consumption. But I don't know how we could actually enforce that on an individual basis.

DR. ASKEW: Dr. Clydesdale has joined our group since we started, and he has a question.

DR. CLYDESDALE: You indicated that you made a number of recommendations. I just wonder if you could tell me how compliance is with those recommendations amongst your group.

MR. McGUFFIN: We believe it's pretty good. We are not an enforcement agency. We don't have any real authority to enforce, and we run into significant conflict or trade obstruction issues if we get too heavy-handed, which really is central to my point. We support the

activity of this group. We really want FDA, through the workings and recommendations of this group, to take meaningful action. We can't enforce these things.

DR. CLYDESDALE: I'm sorry. I must have phrased my question wrong. I asked if you could tell me how much compliance there was, like percent compliance, of your members.

MR. McGUFFIN: I don't know. Actually, the best data that we have is what Connie and Peggy have presented here, that they see that 85 percent of the products in the marketplace have a warning label.

DR. LARSEN: Okay. Thank you.

DR. ASKEW: We had one question. Dr. Marangell wanted to ask a question.

DR. MARANGELL: That was it. Thank you.

DR. ASKEW: Okay. Thank you.

DR. LARSEN: The next speaker is Dr. Michael Davidson from the Chicago Center for Clinical Research. If you would, announce again your name, your affiliation, and who is supporting you for coming here.

DR. DAVIDSON: Good morning. My name is Michael Davidson. I am a physician and a fellow of the American College of Cardiology. I'm an assistant professor of medicine at Rush Presbyterian-St. Luke's Medical Center. I

am also the medical director of the Chicago Center for Clinical Research.

The Chicago Center for Clinical Research performs clinical trials for the food, drug, and nutritional products industries. I have over 10 years' experience as a principal investigator of more than 200 clinical trials in evaluating adverse reactions occurring during the trials.

I have been retained by the National Nutritional Foods Association to review the adverse event reports received by the Food and Drug Administration on ephedra-containing products and to evaluate the recommendations of the dietary supplement trade associations and ascertain whether they are based on appropriate medical rationale.

I evaluated the adverse event reports based on standard FDA criteria. An event was classified as serious if the event was: one, fatal; two, life-threatening; three, resulted in persistent or substantial disability; four, a congenital abnormality occurred; five, resulted in or prolonged patient hospitalization.

The relationship to the ephedra-containing product was classified as: one, unrelated if another cause of adverse event was documented; two, remote if another cause was far more likely to cause the event; three, possible if the adverse event was associated with a potential side

effect of ephedra-containing products, but other causes of adverse event were equally or more likely; and, four, probable if the adverse event was likely associated with the ephedra-containing products.

I have reviewed the Adverse Event Clinical Summaries found at Tab F of your materials. In addition, I also reviewed the case files underlying 191 of these adverse event summaries. Of these 191 case files, I categorized 84 of the events to be serious and 107 not to be serious. Although I reviewed many of the Texas cases, I focused on cases outside Texas as I was advised that others were reviewing these cases.

Of the 84 serious events, I found that 13 were not related to ephedra. I classified eight as unknown for lack of information. Thirty-four were remotely related; 22 were possibly related, and seven were probably related.

Of the 107 non-serious cases, I found that seven were not related to ephedra, and I classified 13 as unknown for lack of information. Nineteen were remotely related. Thirty-nine were possibly related and 29 were probably related to ephedra.

I'd like to review with you the serious adverse events in four areas: number one, death; two, myocardial infarction; three, stroke; and, four, seizures.

There are 22 deaths reported out of approximately 600 adverse events that I reviewed. In my opinion, 12 deaths were either unrelated or remotely related to the ephedra-containing products. Six deaths were possibly associated with ephedra. In two cases, not enough information was provided to consider an assessment. Two deaths were related to consumption of toxic doses of ephedra.

Of the six deaths possibly associated with ephedra, three were due to sudden death and cardiac abnormalities were present on autopsy in all three individuals. Two of the possibly associated deaths were due to strokes. One of these deaths was due to a strong that occurred in an obese individual male who was using multiple other supplements and who had basilar artery atherosclerosis on autopsy. Another was a fatal stroke that occurred in a 44-year-old female due to a left internal carotid artery occlusion. She had a very strong family history of strokes. The sixth possibly associated individual whose death was from a seizure was also on phentaramine, Apidex, a prescription drug for weight loss. All of these six possibly associated deaths occurred on the high-dose ephedra products.

There were ten cases of non-fatal myocardial

infarction. Of these ten cases, four, in my judgment, were not related to ephedra. In another three reports, there was not enough information provided to make an assessment. In three cases of myocardial infarction, a possible association with ephedra exists. In all three of these reports, post-myocardial infarction angiograms revealed normal coronary arteries. All three individuals were consuming high-dose ephedra in combination with caffeine.

There were 17 reports of non-fatal strokes. Three cases were unrelated or remotely related to ephedra-containing products. In four additional cases, not enough information was available for me to make an evaluation. In the remaining ten cases, a possible association with ephedra products exists.

In four of the ten possibly associated cases, these individuals had significant hypertension of hyperlipidemia diagnosed prior to the stroke. One case involved a male with a dilated left ventricle as a possible source of emboli. The remaining five cases involve premenopausal women. At least two of these women were on oral contraceptives. One of these was noted to be a cigarette smoker and the other was diagnosed as having a positive lupus inhibitor. In the three remaining possibly associated cases, oral contraceptive use is unknown and one

was a cigarette smoker, and one of these women was on the product for over a year before she suffered an intracerebral hemorrhage. All but one of these stroke patients--the exception being the woman with a positive lupus inhibitor--were on the high-dose ephedra-containing products.

There were 16 reports of seizures. Of these cases, the majority of seizures occurred in individuals with either a history of seizures or an abnormal EEG on follow-up. As I am not a neurologist, I made only a limited evaluation of these cases.

In summary, with the exception of two cases of toxic exposure to ephedrine, there appears to be only infrequent possible associations of ephedra-containing products with severe adverse reactions. These infrequent possible associations are characterized by coronary or cerebral thrombosis and seizures.

Of the 105 non-serious adverse events that I reviewed, these are characterized by increases in blood pressure, tachycardia, nervousness, and dizziness. These symptoms are expected potential side effects of ephedra-containing products. These side effects appear to be dose-related, occurring in greater frequency in the high-dose ephedra-containing products.

To test the hypothesis that low-dose ephedra

products below 15 mg per dose, which is the recommended dose of the working panel, do not have a significant rate of adverse events, I reviewed the adverse events associated with the ephedra product containing less than 15 mg per dose. These products account for over one-third of all the ephedra-containing products, but only approximately 7 percent of the adverse events. Of these 42 adverse events on low-dose products, there were only two serious events that were possibly related to the product. I mentioned one was the young woman who had a stroke who also had a positive lupus inhibitor, and the other was a 55-year-old female who had a seizure.

Based on my medical review of the ephedra adverse events reports, I have the following opinions:

Number one, last year's recommendation of the ephedra working group and those of the dietary supplement trade associations are appropriate. The two main issues that appear to affect adverse reactions are the dose of the ephedra and the quality assurance of the product.

The proposal to lower the ephedra alkaloid content to 60 mg per day with 15 mg of ephedra per dose, expressed as ephedrine equivalents, provides a margin of safety based on the fact that the vast majority of both serious and non-serious adverse reactions occurred with products that

exceeded these dosage thresholds.

Improved good manufacturing practices and quality assurance will provide dosing consistency within product batches. Because dosing consistency is important, I would add to the recommendation that products that can be easily mis-dosed not be permitted.

The ephedra working group also recommended very appropriate warnings and labeling instructions. I would also include on the label cautions against the use by smokers, those taking oral contraceptives, and those with a history of cardiovascular or seizure disorders.

Number two, clinical data is necessary--

DR. LARSEN: Excuse me. Are you about done?

DR. DAVIDSON: Yes, less than a minute.

Clinical data is necessary to better define the appropriate dose range. Dose titration toleration studies should be conducted which evaluate ephedra blood levels, side effects, and clotting parameters. I have not had the opportunity to determine if such studies have been performed in the past.

Number three, I would also recommend an active surveillance program with approximately 1,000 product consumers in various product categories to better ascertain the frequency and severity of adverse reactions.

In conclusion, I would be happy to discuss with Advisory Committee members and FDA officials my rational with respect to the relationship between the ephedra products and the adverse events. Thank you.

DR. LARSEN: We have time for one question. I want to remind the committee, though, that we do have Mr. Israelson and Mr. Ford at the table if you have questions regarding the industry practices and so forth.

Dr. Ziment?

DR. ZIMENT: Since cardiac disease is the commonest cause of death in the United States, I think we can assume that huge numbers of people have coronary artery disease without knowing about it. How can you give a warning to people who don't know they've got the disease?

DR. DAVIDSON: That is a labeling issue. I think a label also includes issues of--that include many of the major risk factors like hypertension, cigarette smoking, is part of--what I consider to be part of the warning label that would give a higher percentage of people with so-called silent coronary disease.

DR. LARSEN: Time for one more question. Dr. Jasinski?

DR. JASINSKI: Just a comment on this, because nothing you said was surprising, because if you looked at

the data on phenylpropanolamine, it looks exactly the same. If you look at the data on amphetamines from the 1970s from the epidemics in the United States and from the epidemics in Sweden, death as a result of effects on the cardiovascular system are very rare even for amphetamines, relatively few cases, most deaths with essentially sympathomimetic amines with the amphetamines which result in their control as a result of intravenous abuse and infections causing death. So this is nothing that would not be particularly unexpected from ephedrine, which in my estimation is a typical amphetamine-like drug, particularly in terms of it. So I just make that particular comment.

DR. LARSEN: Dr. Inchiosa, did you have a comment?

DR. INCHIOSA: I think your report minimizes the amount of morbidity that is seen. You looked at certain serious events and characterized them or analyzed them. But I was struck with the incidence of adverse effect reporting in a population which is strongly biased against expecting an adverse effect. I think that people taking these dietary supplements have expectations just the opposite of having an adverse effect. And so I think that, if anything, I would anticipate that adverse event reporting is grossly under-reported in people using materials for which they have a positive expectation. And also the numbers are rather

striking. I was struck when there were 330 cases among 100 products that contained ephedrine, and then I received the new data which shows it's over 600 out of a hundred products containing ephedrine, yet the number for all other products is about half that of adverse reports.

So if you just look at it statistically, you have about 600 reports for 100 products containing ephedrine compared with probably 300 for perhaps thousands of other products that are available. So the incidence of adverse effects, morbidity, with ephedrine-containing materials is unassailable in terms of having an association from a statistical standpoint.

DR. DAVIDSON: What I attempted to do is look at it from a dose relationship, and I think the data does speak that if the products contain less than a certain amount, the incidence is similar to what you are describing for all the other supplements out there.

DR. LARSEN: Thank you--

DR. CROOM: Lynn, let me comment. Or do we have another person first on this?

DR. LARSEN: I was going to go on to the next public hearing speaker.

DR. CROOM: Well, I'd like to find out from this person, since we're getting--I need to clarify a little bit

what I think was said last time, because every speaker is bringing up these doses and the amounts.

DR. LARSEN: Excuse me. Will you be available tomorrow to answer any questions?

DR. DAVIDSON: No, I won't.

DR. LARSEN: Is there anybody else that you're associated with that would be able to answer these questions tomorrow? Okay. Dr. Croom?

DR. CROOM: The thing that I'm trying to figure is you're going by the doses, and was that with products with caffeine or ma huang? Or how is that divided up when you had your 15 mg of ma huang? Wasn't that your cut-off?

DR. DAVIDSON: It was just ephedrine. It turns out that when it's a low dose of ephedrine, it's also usually a low dose of caffeine, too. There's usually an association with that.

DR. CROOM: Thank you.

DR. LARSEN: Okay. Thank you very much.

Is Mr. Christopher Grell here? He had expressed an interest, but I did not get a confirmation that he was going to be here. I understand he was on vacation all last week, so I was not able to confirm his presence.

[No response.]

DR. LARSEN: Okay. We will then go on. Is Ms.

Wendy Como here? Wendy Como?

[No response.]

DR. YETLEY: Do you mean Cynthia?

DR. LARSEN: No. There's a little confusion here. We have Ms. Cynthia Culmo from the State of Texas, but we also have Ms. Wendy Como, a consumer who has been affected by these products, from Mishiwaka, Indiana. She was anticipating being here, but I know that they had a financial difficulty, and I'm not sure if she did finally show up.

Well, we'll continue to carry her on the list through the rest of the meeting in case she is able to make it.

With that, we've basically gone through the folks that were assigned to the first session, those who are still in that first session. As I did note earlier, several, at least one person has been moved to a later session, so those sessions will be a little longer.

At this point, I'll turn it back to the Chair, and I think we're a little ahead of schedule, so we will--where I had split our three guest speakers across the lunch hour, I believe we will now have our three guest speakers all before the lunch hour. Back to the Chairman.

DR. ASKEW: And what that means is that Micheline

Ho from Canada will be the last speaker before lunch today.

We're going to take a break now, a 20-minute break. Let's reconvene promptly at 10:20. Those of you that don't know where the restrooms are, follow me.

[Recess.]

DR. LARSEN: Could we have the audience please come to order and the committee come to the table?

I just wanted to clarify one little question that came up at the break. Some of our consultants at the table are new to the committee. Some of the members are new to the committee this time, too. But we try to have enough time during the open public hearing to allow one or two questions at any rate. We don't always get into a full discussion, but if you do have a burning question, feel free to raise your hand and we'll try to get all the questions we can in and work it into the session.

I am looking for Dr. Ziment and Dr. Fong. They're still not back yet? Staff, I guess, will grab them as they come in. Okay.

DR. ASKEW: During the break, the question of over-the-counter drugs versus food products, supplement sources of ephedra, arose again. This continues to be a matter of concern for the committee, and once again, because of the way this is structured, we have to focus here on the

food product or the supplement containing ephedrine alkaloids.

Now, also the question has been raised as to whether or not the OTC drugs are experiencing the same incidence of adverse reaction reports as the food products are, and I think this is probably a fair question. Dr. Shank has indicated that perhaps when Commissioner Kessler joins us later that he may wish to address some of the aspects of the OTC just for people's clarification. But I'd like to try and keep the committee focused on our food supplement sources of ephedrine alkaloids for the purposes of our meeting here.

We're ready now to proceed, and we're going to go into some updates on experiences with these products in Texas and Ohio, and then at the working group, the question was raised: What's the experience of adverse reactions, health problems in other countries? And so we have someone from Canada to talk to us about the Canadian experience.

The first presenter will be Ms. Cynthia Culmo, who is the Director of Drugs and Medical Devices in the Texas Department of Health, and she's going to give us an update on the experience that Texas has had with ephedra-containing alkaloids in food products.

DR. CULMO: Thank you. Mr. Chairman and members

of the Advisory Committee, the Texas Department of Health, on whose behalf I am here to speak, and Dr. Smith, our Commissioner of Health send their regards, as well as our Board of Health. We welcome the opportunity to present comments to the Food Advisory Committee on this important public health issue: the risk posed by unrestricted marketing of drug and dietary supplement products containing ephedrine. Since late 1993, the department has investigated reports of adverse reactions and injuries associated with products containing ephedrine in Texas residents. By the number of products named in the injury reports, sampled from the marketplaces and advertised in numerous medias, we have proof that the quantity and variety of food and drug products containing ephedrine have proliferated in commerce. Many of the products are marketed for indications such as stimulation, weight loss, euphoria, and performance enhancement, for which safety has not been established.

TDH provided oral and written comments in October 1995 to the committee's working group on ma huang. At that time, we indicated that TDH had collected 900 reports of adverse reactions to ephedrine-containing products for Texas citizens; that was 400 from over-the-counter or OTC drug products and 500 from food products. We now have substantially more than a thousand reports of injuries or

adverse events.

The reports came to us from several sources, such as direct reports to TDH, from individuals or their relatives, school personnel, health care professionals, a food product distributor, and Texas poison control centers. As the ephedrine issue gained national attention, TDH also received a number of adverse reaction calls from persons in Alabama, North Dakota, Oklahoma, Louisiana, and other states. These calls were referred to the Food and Drug Administration via MedWatch.

After three years of investigating the health aspects of the ephedrine/ma huang issue, some conclusions have become evident. It may be concluded that ma huang products pose a significant health concern unless used under medical supervision. It may be concluded that the safety of any drug product cannot be separated from the intended use of the product as indicated on the product labeling and promotional materials. TDH is aware of numerous examples of the product distributors, the dietary supplement industry spokespersons, and industry trade organizations which proclaim that ma huang's safety has been established based on thousands of years of use in China. What these individuals failed to disclose is the additional fact that in traditional Chinese medicine, ma huang was prescribed by

a skilled, trained, and experienced practitioner to a specific patient for short-term use for a particular condition and with individualized instructions for use. The most common traditional use for ma huang is to treat respiratory disorders. There is no evidence to show that it was prescribed or promoted for weight loss, athletic performance enhancement, stimulation, or euphoria, as is commonly practiced today. TDH believes the misuse of ma huang products has contributed to the occurrence of the reported numerous adverse events.

Since our last report to the working group, the department has continued to receive reports from individuals, medical professionals, and poison control centers in Texas about problems associated with ephedrine use. In October 1995, we convened a panel of eight TDH physicians and scientific experts to review the information collected up to that date. After a review of the summary data extracted from more than 900 adverse event reports, the panel agreed that the reports containing an alarming number of severe adverse events and numerous less troublesome events which were compatible with the known pharmacological effects of ephedrine alkaloids. The panel agreed that the reports showed strength and consistency of association with consumption of ephedrine-containing products.

The panel recognized and noted the lack of credible scientific evidence to demonstrate a difference in safety between naturally occurring and synthetic ephedrine. Further, the panel acknowledged the likelihood that some individuals are sensitive to low levels of ephedrine alkaloids based on the number of persons who suffered adverse reactions after consuming what was formerly thought to be non-toxic amounts--amounts which we were within the dosage recommended on the product labeling. The panel resolved that ephedrine, both synthetic and naturally occurring, had pharmacologic properties which clearly classified it as a drug and recommended that new rules be written to specifically define ephedrine as a prescription drug and to prohibit its presence in or addition to foods.

In April 1996, the Texas Medical Association convened a medical/scientific panel to review the TDH documents collected up to that date. The panel included two emergency physicians, a psychiatrist, two toxicology experts with experience in substance abuse and poison control, and an ob/gyn specialist. Each of the panel members stated that they were aware of the use and misuse of ephedrine products in their respective practices. The panel agreed that the TDH documents contained numerous serious and less clinically significant adverse events and that there was an established

association of the effects with the consumption of the ephedrine alkaloids. They also agreed that the amount of ephedrine that could be safely added or allowed in foods had not been determined. This was supported by the number of persons who experienced adverse events after consuming apparently low levels of ephedrine in products following the indications and dosages recommended by the manufacturer. The panel resolved that ephedrine and ephedrine alkaloids have properties which categorize them as drugs and that the quality and quantity of data were sufficient to associate ephedrine alkaloids with serious adverse events. The TMA panel recommended that rules be written to define ephedrine as a prescription drug, allowing its use only when supervised by a duly licensed physician.

Based on recommendations of the two medical/scientific panels, on July 26, 1996, the Texas Board of Health proposed rules to place most ephedrine-containing food and drug products on a prescription status. The proposed rules would also prohibit the marketing, advertising, or labeling of any product containing ephedrine for stimulation, alteration of consciousness, euphoria, mental alertness, weight loss, appetite control, performance enhancement, attention deficit disorder, or any other indication not approved by the U.S. Food and Drug

Administration in an over-the-counter monograph or new drug approval. Our 30-day public comment period on the proposed rules will end September 9, 1996.

In addition, a report was authored by the department's Bureau of Epidemiology and the Bureau of Food and Drug Safety and was published in the August 16, 1995, Morbidity and Mortality Weekly Report. I believe the report is included in your book as well as TMA's resolutions.

The report summarized our investigation of adverse reactions associated with ephedrine consumption. In addition, CDC issues a press release on Thursday, August 15, 1996, titled "Herbal Stimulant Drug Can Be Fatal," warning the country that ephedrine can dangerously affect the heart and nervous system.

In conclusion, the department is convinced that products containing ephedrine demonstrate a significant health concern. The fact that 29 states have taken action or have action pending to regulate ephedrine products more strictly than the Federal Government confirms this is the position of most of the nation. Therefore, we believe that action by the FDA to protect the public's health is necessary. We believe that this Advisory Committee should recommend to the U.S. Food and Drug Administration that ephedrine alkaloids be prohibited in foods as food

additives, as foods, dietary supplements, and/or nutritional supplements. The FDA has proposed regulations to remove oral ephedrine drug products from over-the-counter based upon their use in the production of illicit drugs and on their misuse and abuse as stimulants and for weight loss. We believe that safety should also be included as a justification.

As we stated last year, this issue crosses numerous jurisdictional boundaries, and this is a prime opportunity for the state and federal agencies to interact and work cooperatively on an issue of national importance. Once again, we thank you for this opportunity to address the Food Advisory Committee.

DR. ASKEW: Thank you, Dr. Culmo.

A couple of quick questions. Dr. Ziment?

DR. ZIMENT: I'm very worried when people say that doctors alone should be able to prescribe drugs of this nature, because the implication is that you're shifting responsibility to doctors who may not know all these problems, so there would have to be an educational program.

Just to give an example of the dangers of asking doctors to be responsible for prescribing drugs, we heard earlier on from Dr. Michael Davidson of the Chicago Center for Clinical Research that problems occur in many people who

are smokers, who may have atheroma of the coronary arteries. I don't think doctors are going to be able necessarily to detect atheroma in its early stages, and also traditionally ephedrine is given to smokers for the treatment of COPD. So it's going to make it very difficult for doctors to prescribe this drug with the present state of knowledge.

DR. CULMO: We agree. It was also discussed in both panels that there would be an educational effort made. It's not uncommon, if you read the medical records--it's documented in several--that the patients informed their physicians that they were taking these products, and it's actually written down that the doctor said it was fine, these are only herbs, they're not harmful, or it's a dietary supplement and it's okay. So we agree.

DR. ASKEW: Dr. Jasinski?

DR. JASINSKI: You have probably the greatest body of experience of adverse events. I have really a couple of questions about the science. Have you done a classification of adverse events similar to that done by Dr. Davidson? And would your classification be any different than his in terms of--you know, which is the traditional way of classifying adverse events? And, secondly, with regard to the incidence in the poison control centers, how did the deaths relate to what would be other standard compounds, for example, aspirin

deaths, acetaminophen deaths, and how in terms of public health problems to put this is some perspective?

DR. CULMO: I don't have the statistics with me. I actually attended the poison control center's toxicology conference Friday and Saturday in San Antonio, and statistically they commented that still the majority of their calls were for children two years and younger, still a lot of acetaminophen, pesticides, but next to that their calls were on ephedrine products. They have an alarming number of calls, and I don't have those numbers with me, but it's by far the majority of their calls now.

DR. JASINSKI: Would you disagree with Dr. Davidson's analysis for the distribution? Was your data any different than his analysis of the adverse events, I mean in terms of his classification relationships with deaths?

DR. CULMO: Yes.

DR. JASINSKI: In what way?

DR. CULMO: We disagree. When we looked at it, he has several that he says not associated or unknown. Every one of our reports--it's documented that there's a common link. There's a common thread throughout all of these adverse events and that every one of these persons was taking an ephedrine product.

DR. JASINSKI: But that's associated, and being

causal and associated is different. People, young people--I mean, it's always a problem. A certain percentage of young people are going to die from strokes or some unexplained cardiac event, and it's associated. People classify this all the time. Have you guys actually done this and classified it to look at this and compare it? Or have you just tabulated this, or have you done some sort of analysis on this data?

DR. CULMO: It's tabulated. It hasn't actually been broken down. But, again, we keep saying associated. I don't believe we've ever gone on record and said caused.

DR. ASKEW: Dr. Georgitis?

DR. GEORGITIS: In your review of the adverse event reporting, what were the combination products with caffeine containing in addition to the ephedrine versus just pure ephedrine alone?

DR. CULMO: The numbers?

DR. GEORGITIS: Specifically, was it--because you have over a thousand cases. Is there any way you can give me a percentage?

DR. CULMO: Gary, do you know what it is off the top of your head?

This is Gary Coody, the senior pharmacist in our division, and he has most of the technical knowledge on

this.

MR. COODY: Again, over the more than 1,000 cases included the drug product also, and so probably about half are synthetic ephedrine drug product. But most of the food supplement products--I don't have a percentage--I would say it's 90 percent contained caffeine also. They were combination products.

DR. GEORGITIS: Along the same lines, since you've reviewed the data, could you comment on the description of the adverse events versus OTC and the nutritional supplement?

MR. COODY: Well, the difference in the drug product adverse events are generally that most of the drug product adverse events are results of abuse. They're mainly younger people who have taken much more than indicated on the OTC monograph, and they have either gone to the emergency room or been admitted to the hospital because of palpitations or other, you know, self-limiting conditions where they actually were treated and released. The food supplement products, however, were generally taken by older people, you know, 30s and 40s, and those reactions generally were--

[Laughter.]

DR. ASKEW: Thank you.

MR. COODY: Yes, but the types of events are the same. I think the difference is that in the younger population with the OTC drugs, we don't have as many serious events documented, because they're poison control calls.

DR. ASKEW: Thank you very much. We need to move on to the Ohio experience now, and I'd like to introduce Dr. Frank Wickham from the Ohio Board of Pharmacy who is going to give us a summary of the Ohio experience.

Also, for those of you that didn't get a chance to ask a question, at the end of all three of these presentations, we'll have another question-and-answer period. So if you have something, why, you'll get a chance.

MR. WICKHAM: Mr. Chairman and members of the Food Advisory Committee of the FDA Center for Food Safety and Applied Nutrition, my name is Frank Wickham, and I have the honor of serving the citizens of Ohio as Executive Director of the Ohio State Board of Pharmacy and have done so since September of 1977. I wish to provide you with information regarding the Ohio State Board of Pharmacy and its responsibilities as an agency of the executive branch of state government prior to discussing the Ohio experience with ephedrine. I have given to you a packet of material, a copy of my testimony here, along with supporting documents. I apologize if it doesn't make sense. Hopefully it does. I

ended up writing it Sunday afternoon after having been operated on Saturday afternoon and under the influence of painkillers and dictating it to my 25-year-old daughter who put it into the computer for me. So hopefully it does make sense, and I will be here for the next day or so to answer any questions you may have, I guess today and tomorrow.

First of all, the Board of Pharmacy is a state agency under the executive branch, and my members are appointed by the governor. The Ohio Board of Pharmacy was created by the Ohio General Assembly in May of 1884 for the purpose of ensuring that individuals practicing the profession of pharmacy were qualified by education and training to practice their profession. Since then, the Ohio General Assembly has gradually expanded the board's authority and scope of responsibility by mandating that the board also administer and enforce all of the laws governing the legal distribution of drugs in the state of Ohio. In other words, we're sort of a one-stop shopping center regarding drug laws in the state.

As the single state agency for drug laws in Ohio, we're responsible for not only administering and enforcing the Pharmacy Practice Act, but also the Dangerous Drug Distribution Act--these are drugs which are prescription only or drugs which are Schedule V controlled substances or

injectables for human use--the Hypodermic Act, the Pure Food and Drug Act, Controlled Substance Act, and the Criminal Code Chapter on Drug Crimes.

The board consists of nine members, eight of whom are pharmacists and represent different areas of pharmacy practice, and one who is a public member who is at least 60 years of age.

I might note her our board meets approximately anywhere from 40 to 60 days a year carrying out their statutory responsibilities in the state at meetings in Columbus, Ohio.

At the present time, two of the pharmacist board members practice in long-term care facilities, and their practice involves the daily review of the drug regimens of patients residing in nursing homes and assisted-living facilities. These patients not only include the elderly but also those patients requiring assistance in living due to a physical, mental, or developmental disability. Four of the pharmacist board members represent community pharmacy practice, while the remaining two represent pharmacy practice in hospitals and community ambulatory clinics.

One of the most important responsibilities of the board is the administration and enforcement of Ohio's Controlled Substance Act. This act gives the board the

authority and responsibility for adopting rules for the administration and enforcement of Revised Code Chapter 3719 and for prescribing the manner of keeping and the form and content of records to be kept by persons authorized to manufacture, distribute, dispense, conduct research, and prescribe, administer, or otherwise deal with controlled substances.

The act provides that the rules adopted by the board shall: number one, facilitate surveillance of traffic in drugs to prevent the improper acquisition or use of controlled substances or their diversion into illicit channels; and, two, aid the state board of pharmacy and state, local, and federal law enforcement officers in enforcing the laws of Ohio and the Federal Government dealing with drug abuse and control of drug traffic.

The board also has the authority to add, transfer, or remove a compound, mixture, preparation, or substance from the schedules. The board may also classify any non-narcotic substance that may be sold over the counter without a prescription, pursuant to the Federal Food, Drug, and Cosmetic Act, as a prescription drug should a pattern of abuse develop.

I have included several documents for your information with written copies of my testimony before you

here today. The first document consists of nine pages and provides you with a brief biographical sketch of the members of the Ohio Board of Pharmacy, marked as Exhibit A. These individuals are practitioners of a profession that deals with the misuse and abuse of drugs on a daily basis. They are also members of a profession which is business and marketing oriented. Accordingly, they have the experience and expertise to readily recognize the promotion and marketing of products that have been and are misused or abused by the public. They, like you, are also citizen volunteers and take their responsibilities seriously in carrying out their statutory duties. Each of the nine board members are parents or grandparents and are well aware of the dangers associated with drugs and their abuse or misuse, not only by young people but young adults.

The second document is a "Controlled Substance Act Drug Abuse/Misuse Report on Ephedrine," Exhibit B. This report provides you in detail Ohio's experience regarding ephedrine and ma huang since the first indication in July of 1993 that products containing ephedrine were being abused and misused by "kids" and "adult drug abusers" in Ohio. The report is complete through March 13, 1996. Unfortunately, we haven't had the staff or the time to update it since that date. However, this document has been of such tremendous

interest to so many people, we might mention the fact that it is on our home page on the World Wide Web, and as we do update it, you may be able to access that and download it for your information.

The report also does not discuss any of the political issues and activities surrounding the Ohio experience with the drug ephedrine. My testimony here today is to bring you up to date with what has happened since March 3, 1996, and inform you about what has happened politically regarding this issue.

First of all, one of the biggest surprises regarding this issue was learning about the Dietary Supplement Health and Education Act of 1994 at a public hearing being conducted by the board. While the board is responsible for enforcing all the drug laws in the State of Ohio, for some reason or another we really weren't quite aware of the fact that there was legislation making its way through Congress known as the Dietary Supplement Health and Education Act of 1994. The purpose of the hearing where we first heard about this was to adopt rules implementing Ohio's legislation placing ephedrine into Schedule V of Ohio's Controlled Substance Act, and I heard some questions here earlier by one of the panel members about has this been addressed as far as the standpoint of the controlled

substance law. This is how it was addressed in Ohio.

At that hearing, testimony was given by Mr. Anthony Young, here today, general counsel of the National Nutritional Foods Association, that "dietary supplements are not drugs; they are foods." Mr. Young further stated that Congress defined dietary supplement products as not being drugs.

Subsequent to the hearing, a copy of the federal law was obtained, and the board members were astonished to learn that any product containing a drug could be labeled by its distributor or manufacturer as a dietary supplement and could not be considered a drug under the Federal Food, Drug, and Cosmetic Act. Therefore, products labeled as dietary supplements could not be subjected to the safety and efficacy provisions of that law.

Following the hearing, the board adopted regulations implementing Ohio's law placing ephedrine into Controlled Substance Schedule V. The purpose of these rules is to prevent the improper acquisition or use of products containing ephedrine regardless of its source--natural or synthetic. Our board does not differentiate between the two. Enclosed with my materials are two documents. The first is a summary of the laws and rules regarding the legal sale of ephedrine-containing products in Ohio, Exhibit C.

In reviewing that, you will find that we did not ban the product sale in the State of Ohio, but what we did do, we limited their sale under the supervision of a pharmacist as a Schedule V over-the-counter controlled substance, much like the cough syrups. In those rules, we adopted regulations similar to those adopted by the Federal Drug Enforcement Administration, United States Department of Justice, where it was illegal to sell such products to anybody under the age of 18. And I think you're well aware of Pam Richardson, who was not able to be here today, but Pam's son, of course, Carl, was the individual whose death resulted in the law in Ohio placing ephedrine products into Schedule V of the Controlled Substance Act.

The second document is a summary of the penalties for violating provisions of these laws and rules, Exhibit D.

It's very interesting because one of the things that led up to our discussions, we were approached by the Senator representing--well, Pam Richardson was a constituent of this Senator, Senator Kearns--her legislative aide and an intern had approached us saying we've had this death of this young man due to a toxic level of ephedrine, taking it, of course, not having any idea that the product was dangerous and such, and what can we do about.

During our discussions, we talked about--well,

there were several things. Number one, the board is looking already under its previous authority to put it on prescription only. But we had some problems with putting it on prescription only. It was also mentioned by panelists here about the educational aspects of doctors, and we're very much aware of the fact that most of them didn't know what ma huang is or the fact that ephedrine was an active ingredient of the drug known as ma huang. As a matter of fact, during many of our conversations with people calling in with bad experiences with products, they said, well, we talked to our doctor and our doctor said it was perfectly safe to use because it was being sold over the counter, therefore you should not worry about it and you shouldn't hesitate to use the product. So automatically because of the laws we have in place with over-the-counter drugs, the doctors assumed that it was, in fact, a safe drug and did not contain anything like ephedrine, a very strong sympathomimetic agent.

The other reason for going with this law is that we're a small agency. We have 40-some employees; 20-some of them are out in the field as investigators, and we license over 12,000 sites that distribute drugs in the State of Ohio, as well as other 12,000 pharmacists who are practicing pharmacy in the State of Ohio.

Following widespread publication of the rules and extensive coverage by the press, both newspaper and television, placing ephedrine into Schedule V, and we had emergency--there was emergency legislation as well as the fact that we had some emergency rules through the governor's office to put the law into effect, the board office was inundated with telephone calls, petitions, and form letters from multi-level distributors of products containing ephedrine that were labeled as dietary supplements. We were shocked. We really didn't realize. We had gone through our database. We maintained a database of all the products that had been approved by the FDA for approval for sale in the United States as either over-the-counter or prescription drugs, and we didn't identify any of these products. But we come to find out that there was a tremendous number of them out there.

Included in your packet of materials are examples of these form letters and petitions, Exhibit E. These distributors also forwarded their petitions and form letters to elected officials in Ohio.

I might relate to you, of course, a lot of this, like many things, is about money. We were very much surprised, number one, when we started getting calls when this information hit the press from individuals from beauty

salons, saying nobody told us that this product that we're selling contains a drug, ephedrine, that could be dangerous like this, and, therefore, we do not want to continue to sell it. Is it true and what kind of information can you provide us regarding it?

It was interesting in talking to those individuals because it was $6,000 to $8,000 worth of products they were selling a month. So it was very significant.

Also much to our surprise, we had a young man who called and had just purchased a General Nutrition, GNC, franchise, and he said, Do you really realize what happened, what you've done to my business in the State of Ohio? And in talking to him, we said, well, no, we really don't. We don't know anything about these types of products that are on the market; we have no way of getting information about them. But he related to us that approximately 45 percent of the products, he estimated, in the franchise store essentially did include ma huang or ephedrine in one form or the other.

One of the interesting things politically employed by a health store manager from a neighboring state was to encourage his customers to return their empty supplement bottles to his store, and these bottles would then be shipped to the governor's office, along with Exhibit E. And

I think you might find it interesting to read that document because this is sort of what we're hearing from many of the people out there regarding: When can we start selling this product again? How soon will it be back on the market?

Discussions with many of the individuals calling the board office about dietary supplement products containing ephedrine disclosed not only the fact that many of them were being sold through multi-level distributors, but we also learned that many of them were making $10,000 a month or more by selling ephedrine-containing dietary supplements. We even had one entrepreneur who had these very fluorescent signs--I don't know whether you've seen any of them around here or not, but they're in pink and green, and they would say, Imagine, make $10,000 a month or more, call a 1-800 number. And, of course, you call that number and essentially it was sort of like a franchise for selling these products for weight loss.

The board has attempted to compile a comprehensive list of all products containing ephedrine in either its natural or synthetic form. To date, the board has identified over 205 products. We have enclosed with your material a list of those products, the name and address of the distributor or manufacturer, and information pertaining to the source and quantity of ephedrine in the product. And

those are Exhibits F and G.

Let me preface my remarks by saying that these forms--I did not get to put it on there in a key, but essentially that information either came from advertisements of these products in publications such as muscle building magazines, what have you, or bikers' magazines, and also from the labels of the products that we were seeing in our office that were being provided to us by individuals for additional information about them.

Legislation was introduced in both the House and Senate during this session of the Ohio General Assembly. The Ohio General Assembly runs for two years. It's continuous in the State of Ohio. And so on January 1, 1995, our present General Assembly was reconvened and they'll be running through this year, December 31st of 1996. We have included in your material here a copy of Substitute House Bill 523, a Legislative Services Commission Analysis of this bill, and an excerpt from the "Ohio Report" of Gongwer News Service, and these are Exhibits H, I, and J. I put these in here because I think it's very important to you as an Advisory Committee to the Food and Drug Administration about the safety and the use of these products on the market as dietary supplements for weight loss.

Please note that this legislation relies on FDA's

decision as to the quantity of ephedrine and duration of time that ephedrine may be used without being hazardous to a person's health. It's up to you, it's up to the FDA to make that decision. We think rightfully so it should be in your hands.

Let me just tell you to date, though, however, under Ohio's law we do have the authority, the board has the authority to accept products from Schedule V of the Controlled Substance. In other words, a petition is submitted to the board. The procedure for submitting that petition is in your packet there, and we're looking at it from the standpoint: Does the labeling, the way it's being promoted and such tend for the product to be abused or misused by the individuals who are using it?

If the board feels that it's not, does not have a tendency to be misused, then the board can approve it for sale by any outlet in the State of Ohio. To date, the only product that the board has approved for sale outside of a pharmacy or under the supervision of a pharmacy is a Schedule V controlled substance, essentially, as traditional medicines, is Breathe Easy Tea over here, the reason being that the board felt very comfortable with the fact that, based on the information provided to them in the petition, it contained no more than one-quarter milligram of ephedrine

per cup of tea. And, of course, it was being promoted for the purpose of breathing problems. It's traditional, been on the market for many years, and we had no indication that it would be abused or subject to abuse.

In closing, just let me make one other comment, and that is, as the single state agency responsible for all these drugs laws in Ohio, there is no other group of drugs where we have greater problems or potential for abuse than those products for weight loss or as stimulants. Time after time we talk to individuals, and they always feel that more is better, number one. We are at the present time--and I can go into this later on if there's any questions regarding this, the board did exempt pseudoephedrine products. We now have a reported death associated with the use of pseudoephedrine, because once we took and excepted pseudoephedrine products from the Ohio's Controlled Substance Act Schedule V, one of the manufacturers immediately came out with a product called Mini-Thin Pseudoephedrine. And so we now have that as a problem among school children using it, as well as adults using it, and one reported death associated with the use of pseudoephedrine at this point.

So weight loss products are very serious. We tend to find that those people who are seeking to lose weight, of

course, have a lot of health problems and probably have been using a lot of products, especially controlled substances, in trying to control their weight.

At this time I'd be happy to respond to any questions that members of the committee may have. As I said, I will be here for the next day or so, too.

DR. ASKEW: Thank you, Dr. Wickham.

Does the committee have any questions to address to the speaker? Yes, Dr. Marangell?

DR. MARANGELL: What's happened subsequently in the last two years since you've implemented your new policy with Schedule V? Have you had decreased reporting of adverse events?

MR. WICKHAM: Yes, we have. We've had decreased reporting of adverse events. The law has worked very well. Many of the people who were selling the product through multi-level distributorships and such have been very responsible and have not sold them in Ohio. There are still a few people out there, of course, but the majority have not. So the number of calls has decreased significantly.

DR. ASKEW: Yes, Dr. Jasinski?

DR. JASINSKI: I hadn't seen this. Going back to the epidemiology and the science, in this document on the drug abuse/misuse report, what you used as the basis

primarily for this was the DAWN data on national data. Your data from in-state from death, et cetera, are relatively few, and they were associated--I think there's only one death at the back of the report.

What I don't understand is if you look at the DAWN data that you quoted, pseudoephedrine was much greater a public health problem, two to three times by my estimate, as ephedrine, yet you control, you exempted pseudoephedrine when the DAWN data which was used for the basis shows it's two or three times the incidents and emergency rooms and death. Could you go through that?

MR. WICKHAM: Yes, Dr. Jasinski, that was a result of a political decision and based upon pressure brought upon the sponsor of the original legislation. I was on vacation during that period of time, but I got a call from my office saying that my staff and some of my--the board president had been called into the governor's office, and the legislator was there who sponsored the original legislation, that they did not intend to address pseudoephedrine products so therefore it should be excepted.

DR. JASINSKI: Well, I mean, cynically, the health food stores make money selling ephedrine-containing products. The drug stores with the pharmacists make their money by selling pseudoephedrine-containing cold products,

if you want to look at this cynically. Is this politics?

MR. WICKHAM: I don't think it has to do anything with cost as far as our decisions were concerned, but I think that that is part of the politics as far as the market is concerned, yes. The number of pseudoephedrine products out there are significantly high, and they're in accordance with the monographs issued by the Food and Drug Administration for the legitimate use as over-the-counter drug products.

DR. ASKEW: Dr. Ziment?

DR. ZIMENT: A few years ago, phenylpropanolamine was one of the most frequently used drugs in this certainly, and I think a lot of it was used for dietary purposes. Do you have any information, number one, on how effective this drug is for dietary purposes compared to ma huang and ephedrine? And, number two, do you have information on side effects of a serious nature resulting from use of phenylpropanolamine? And, number three, what controls would you advise for phenylpropanolamine?

MR. WICKHAM: Number one, I do not have any evidence or indication about how effective it is as far as weight loss control is concerned. I will say that I think that we've stopped having as many problems with phenylpropanolamine as these other products became more

available and much more accessible. So I think people have gotten away from the phenylpropanolamine products. In talking to pharmacologists and drug information centers and such, they do have some very serious concerns about the adverse effects of the phenylpropanolamine products and that there are cases of abuse out there, but they're just not in large numbers as they are for the other products because something more popular is out there now.

What type of control? That's a good question. If these products, I think, were going to remain--you know, we need to look. We're talking about health care in this country and costs. We've got to stop looking at the trees and start looking at the forest, and it's all of these many different factors that are increasing our cost of health care.

You look at the NIDA data about the emergency room visits, and I don't know what they say about the cost of emergency room visits. I sometimes think that's exaggerated. But it's phenomenal. And that DAWN data is very limited as to the parts of the United States that it covers, mostly large metropolitan areas. So I think we need to take and have somehow procedures in place for more responsible use of drugs, not only prescription drugs but over-the-counter drugs. There needs to be more of an

educational effort.

DR. ASKEW: Dr. Israelson, and then Dr. Dentali.

MR. ISRAELSON: Just a follow-up comment from your remarks, Mr. Wickham. Any product containing the drug could be labeled by its distributor or manufacturer as a dietary supplement. That, of course, is a repeat of our previous comment. It really concerns us. That certainly was not the intent of DSHEA. I don't believe that's what the law reads.

Is that still your impression in Ohio?

MR. WICKHAM: Yes, it is, and the reason, it's not so much maybe whether that's what the law reads or the intent of the legislation, but that is the practicality as far as trying to get a prosecutor to take a case based upon the law being in place.

MR. ISRAELSON: Do you have other examples of products that are masquerading dietary supplements which you regard as drugs?

MR. WICKHAM: Well, I think that there will be-- there are some, yes, and there's more coming on the scene. One is the new product DHEA. We've got a situation going on in the State of Ohio now with that.

MR. ISRAELSON: Any others that you could specify?

MR. WICKHAM: Not at the present time that I'm aware of any adverse reactions and such. I think it's a

very interesting phenomenon, this whole issue of melatonin, and we are getting some adverse reports on that, but not to the extent that we've had with ephedrine and such.

DR. ASKEW: Dr. Dentali?

DR. DENTALI: There are certainly gray areas involved in here, and I'm acutely aware of that, having trained basically as an herbalist who can go out and collect plants and identify them in the field and make medicinal products from them and having participated in drug isolation and discovery work on natural products.

Epinephrine is a related compound. My heart beats about 100 beats per minute now, so I ask your indulgence a little bit while I express myself here, because I don't want to be an adverse event from that substance.

I feel there are some lines being blurred here. We're here to look at food products containing ephedrine alkaloids that are being sold as dietary supplements, and I think it's important that we keep in mind that if they're products that are indeed not dietary supplements that are being sold as dietary supplements, that the agency be strongly encouraged to take some action against that.

I would like to see us here on the committee keep in mind that there are products that are appropriately dietary supplements and that many of the things here we're

being asked to consider today are products that are being sold as dietary supplements and are, in fact, not dietary supplements.

I think that's a very important distinction that we need to keep in mind so that we can address that. Yes, there are situations here where these products are being inappropriately marketed. They're either adulterated or mis-branded, and that action needs to be taken against those so that we can look at products that are dietary supplements and the safety and efficacy--or the safety regarding those materials.

Also, as we're talking about products that contain ephedrine alkaloids, it's also important we keep in mind the distinction between products that are extracts and that are, again, appropriately a dietary supplement and those that are pure ephedrine, whatever the source, and that we're able to look at the adverse reactions in those cases and determine which ones are indeed a single, isolated, purified ingredient that would render those mis-branded and others that are indeed herbal extracts.

Thank you.

DR. ASKEW: Dr. Woosley had a comment.

DR. WOOSLEY: A couple of people have referred to or alluded to the ability of physicians to be familiar with

ephedrine. I'd like to respond to that.

In the four medical schools I've been affiliated with, ephedrine was regularly taught in the pharmacology course for physicians. Ma huang was regularly mentioned in every course I've been affiliated with. And ephedrine continues to be on the list of drugs that the Society of Pharmacologists, Medical School of Pharmacologists, recommend for educational purposes. Ephedrine is listed as a drug that should be taught.

The reason it should be taught is it's a very potent drug. It's a drug with a long history and one that we understand quite well. And so I would conclude that doctors are familiar with ephedra.

More importantly, though, I think doctors will make a distinction--or make a determination of potential medical value for that patient, and I think that's something that has not been considered in the discussions before. And I think anytime a drug is administered, which this is, a medical value has to be part of the equation.

The other very important point today that has changed in the last few years is that there are medical alternatives. There are drugs that are medical alternatives that can provide medical value; whereas, perhaps 50 years ago or even 20 years ago, those were not readily available.

Those are my comments at this point.

DR. ASKEW: We are going to have an opportunity at the end of the three speakers for further comment, and also there will be plenty of time tomorrow for general discussion. I would kind of like you to limit it to specific questions of the speaker rather than general comments at this point in time. So if you wouldn't mind holding your questions until after we have the speaker from Canada, then we can have further comment at that time.

Thank you very much, Dr. Wickham.

I'd like to move on now to Dr. Micheline Ho, Chief of the Product Regulation Branch, Health Protection Branch in Health Canada, from Ontario, who will tell us a little bit about Canada's experience. Dr. Ho?

MS. HO: Good morning, everyone. Mr. Chairman, members of the working group and committee, I am pleased to be here to represent Canada and tell you a little bit about our position on this issue and how we got there, even tell you about the problems that we ran into with respect to this issue.

First of all, a point of clarification. I am not a doctor. I started out as a chemist, with further academic training in pharmacology and business administration during my tenure at Health Canada. This is my title: I am Chief

of Product Regulation Division. The bureau is now called Bureau of Pharmaceutical Assessment. We have joined the Bureaus of Non-Prescription Drugs and Prescription Drugs recently, so we now have a new name.

The Health Protection Branch is the level that is about the counterpart of the FDA, and this is all part of Health Canada. My responsibilities are mainly in the area of non-prescription drugs.

The next overhead will show you a brief summary of what I will be addressing. First of all, a little bit about the legislation, some definitions, the premarket authorization scheme for drug products, traditional herbal remedies, the history of ephedra, and a short conclusion.

First of all, the legislation. At the moment, products intended to be ingested in Canada fall into two categories. They are either foods or they are drugs. The legislation, the Food and Drug Act and regulations, defines these two product categories. Food is defined as a food as well as--this could be read food is a food and it includes any article manufactured, sold, or represented for use as food or drink for man, including chewing gum, and any ingredient that may be mixed with food for any purposes whatever.

The next will be the definition of a drug. It

starts the same way. A drug includes any substance or mixture of substances manufactured, sold, or represented. A and B are the two paragraphs that are of interest today: the diagnosis, treatment, mitigation, or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof in man or animal, or B, restoring, correcting, or modifying organic functions in man or animal. The third part is really for disinfectants.

I would like to draw your attention to the fact that the definition, again, starts with the word "includes," and this is being interpreted, again, as meaning that a drug is a drug. And the definition is used where there may be a doubt as to the classification of the product. But if the product is obviously a drug, as everybody would know that to be, you don't need to use the definition. It's a drug. And we have the same thing for food.

I would also like to draw your attention to the fact that the definition does not refer to the source of the ingredient, whether natural, synthetic, or whatever origin. It's immaterial.

I also draw your attention to the term "manufactured for," which can be interpreted to mean that if there is a single known purpose for the use of a product manufactured or sold, that purpose being for a therapeutic

or medicinal use, the definition will apply, even in the absence of specific representation of therapeutic use.

From the definition of drug, we can clarify two main criteria for the classification of products as drugs. One, does the product have pharmacological effect? And, two, is it sold or manufactured with therapeutic or medicinal representation? Either criteria will suffice to clarify the product as a drug. In the case of ephedra, the substance in sufficient quantity is known to have pharmacological effect. It is therefore under such circumstances classified as a drug.

In most cases encountered in Canada, preparations containing the substance ephedra were either labeled or represented in advertisements for therapeutic purposes, thus again meeting the definition of a drug under the act. Representations found in relation to products marketed without premarket authorization included aid to weight loss, stimulant, just like you have here, or aphrodisiac, that kind of representation. As an aid to weight loss, the only possible explanation for the action of ephedra would be due to its stimulant effect, as the product is not, in fact, a calorie-reduced meal substitute, nor is it recognized as an appetite suppressant. In the latter case, it would be a therapeutic effect, anyway, and it would be considered to be

a drug.

A product which provides energy can be a food if the energy is in the form of a calorigenic source. However, when the energy is to be derived from a few grams or milligrams of herbs, the effect can only be from a substance having pharmacological effect.

The difficulty in supporting the drug classification when a product such as ephedra is marketed without therapeutic representation surfaces when the manufactured product contained ephedra in very small amounts. In cases where no representation of therapeutic purposes is made and no pharmacological effect can be ascertained, the history of use can be a factor in the classification decision. As mentioned earlier, the definition of drug provides for an intended purpose for which the drug is manufactured or sold.

An argument can be made that the simple mention of the substance ephedra on a label or in an advertisement could be considered as a therapeutic claim if there is sufficient information disseminated to the public to the effect that ephedra has a pharmacological effect for its intended purpose as a stimulant, a substitute for "ecstasy," an amphetamine congener, or an aid to weight loss. This is particularly true if there is no history of use of the

substance as a food. This type of argument is also used to classify fluoride toothpaste as a drug. The simple mention that the toothpaste contains fluoride is understood by the public to mean that the product will have anti-cariogenic properties and, therefore, is a drug product.

I will go into more details a little bit later on about ephedra. I would like to talk a little bit now about the premarket approval scheme for drug products in Canada.

The regulations under the Food and Drugs Act currently requires that all drug products offered for sale be subject to a formal approval prior to marketing. Under the current scheme, there are two broad categories of submissions: first, the new drug submissions or new drug classification, and all other drug products fall into the other category. New drugs are defined as products which have not been sold in Canada--next overhead, please--for a sufficient time or in sufficient quantity to establish the safety and efficacy of the drug in Canada. I believe that's fairly similar to the U.S. legislation.

For a new drug application, the regulations require full data package, preclinical, clinical data, chemistry, manufacturing. For products that are not new drugs or preparations for which an application for a drug identification number is required, the type of data to be

submitted varies with the product type. The latter category is quite broad; that is, the non-new drug groups. It includes most OTC drugs; vitamin and mineral preparations, which are drugs in Canada; homeopathics; and traditional herbal remedies.

Now, because ephedra is a drug, I will concentrate on the traditional herbal remedies issue.

Generally, the legislation requires that drug products marketed in Canada be demonstrated as safe and effective. However, the safety and efficacy requirements which are applied depend on the product type. The specific product types are not described in the legislation, so we operate under administrative interpretation. We do try, however, to the extent possible, to publicize these administrative interpretations to assist the industry in finding appropriate submissions, as well as to ensure consistency in the agency for the application of this interpretation. One such interpretation is that which is applied to traditional herbal medicines.

In order to permit the marketing of such preparations in Canada, we could not have applied the requirements applicable to new drugs. This would have precluded the marketing of the product class altogether and would also be seen as an unreasonable approach.

Unreasonable because not all, although many, of the preparations have, in fact, been used for many years without evidence of safety concerns. Unreasonable also because it would be denying access to a class of products which the general public may wish to employ. Our role in this issue is to ensure that the drug products available are safe when used as directed, and in terms of efficacy for this product class, that the product is aware--that the efficacy is established on the basis of traditional use as opposed to on the basis of current scientific standards which is applied to new drugs.

In lieu of applying new drug regulations, criteria for applicability to traditional herbal remedies were established and provided to the industry in an information letter in 1990, and I have a copy of that document if you are interested in retaining that. This document indicates that herbs may be sold either as food or as drugs. We all drink tea or coffee, and we use herbs to add flavor to our foods. There are legitimate food uses for herbs.

When used as food, however, herbs should be sufficiently safe that they can be consumed by just about anyone and more or less at will. This is not the case for all herbs, obviously. Some herbs are very toxic even in small amounts. Deadly nightshade, mistletoe, nox

pharmaca(?) are examples of herbs that are toxic even in small amounts. These should not be sold as food. This doesn't mean that such herbs should automatically be classified as drugs either. Toxicity is not criteria in the classification.

Although the Food and Drugs Act contains a general prohibition on the sale of food that is unsafe, it is often advisable to specifically mention prohibited substances in the regulations. This serves to alert producers to the inherent risks posed by specific substances and also facilitates the work of monitoring the market to ensure that such unsafe foods do not enter the marketplace.

At the moment, there are very few such substances specifically prohibited by regulation. In view of the increased interest in the marketing of herbal preparations, concerns have arisen which have led the department to propose that a number of toxic herbs be prohibited from being marketed as foods in Canada. A list of approximately 65 herbs has been proposed for consideration as adulterants when sold as food or in a food. The substances mentioned earlier are on that list. Ephedra is not on the list at the moment.

Whether or not any of these substances may be sold as food--as drugs, excuse me, is what I will be discussing

next. What are the criteria for acceptability as traditional herbal medicines? These criteria will include whether the product is appropriate for self-medication since the industry is interested in selling these products over-the-counter. We will look at safety, efficacy, and labeling.

In terms of self-medication, we have used definitions for these terms, again, to assist the industry in determining what the agency would consider appropriate indication for over-the-counter use for all over-the-counter products, and we have used that to apply it to traditional herbal remedies. We have broken down self-medication into three parts: first of all, the self-limiting condition, self-diagnosis, and self- treatment.

The next overhead, please.

We have defined a self-limiting condition as a condition that, if inappropriately treated or left untreated, would generally not lead to serious consequences; a condition that generally resolves within a limited period of time without treatment; and the third criteria is simply there to not exclude from the category products that are for prophylactic use, such as vitamin supplements and mineral supplements and anti-caries preparations.

We have also defined self-diagnosis as a situation

where the patient or guardian can accurately determine the condition, monitor the severity of the condition, and have some ability to differentiate whether professional assistance is required.

And self-treatment, a situation where the patient or guardian can appropriately select and use the treatment, can monitor for positive and negative effect or lack of effect of that treatment. And the last condition relates to prophylactic use as well.

In addition, in relation to the appropriate indications for non-prescription drugs, the legislation has under Schedule A a list of conditions which are considered to be inappropriate for self-medication. Next overhead, please.

This is obviously a list of the more serious medical conditions, conditions for which the patient can usually not self-diagnose or self-treat for various reasons. So these are inappropriate for any over-the-counter products and also inappropriate for over-the-counter medications--for traditional herbal remedies.

In addition, in order to reduce the risks associated with traditional herbal remedies, we have required that the indications be very specific. We have not accepted vague terms such as tonic, alterative, or dietary

supplement. The condition or symptom to be treated has to be very specifically mentioned.

In terms of safety, as the products are generally intended to be freely available in the marketplace for purchase by consumers without the assistance of a health professional, safety was the major concern. The products would not be accepted if serious safety concern existed with any of the substances, and if these concerns could not be adequately controlled, such as by labeling. While it is essential that foodstuffs be sufficiently safe that they can be consumed in unrestricted amounts, certain levels of risk can be accepted for drug products depending on the benefits anticipated. So far, it has been determined that certain herbs hold such a level of risk for non-prescription drugs that these risks overweigh any potential benefit. These include germender(?), chaparral, and some species of comfrey, and these products have not been authorized in any non-prescription drugs for sale in Canada.

In terms of efficacy, as we have determined that the new drug provisions could not be applied to this product category, a different set of criteria than required in clinical studies to today's standards had to be established. The requirement imposed is that the sponsor should provide two references from the traditional herbal literature in

support of the use of each herb in the formulation proposed and in support of those that recommend it. Provided that more recent data did not contradict the references provided and if the other criteria such as safety and appropriate for self-medication were met, the indication was being accepted. Those such references must be appropriate for the part of the plant used and for the form in which it is used.

In terms, again, of controlling the risks that may be presented by these types of preparations, we have also required some labeling information. The general criteria is that the product be labeled as traditional herbal medicines to clearly indicate to the general public, again, that the efficacy of these products is based on tradition. Further, if there are any interactions, food-drug interactions, any contraindications, precautions, and warnings, these also have to be placed on the labeling material.

I will now talk a little bit about the history of ephedra in Canada.

Because ephedra is an herb, it has been considered, obviously, under our traditional herbal medicine policy. The sale of ephedrine and pseudoephedrine, the main constituents of ephedra as OTC in cough and cold remedy, was already permitted in Canada when the traditional herbal medicine policy was established. A few years ago, an expert

advisory committee was established to review and formulate recommendations concerning non-prescription drugs for cough and cold. The committee looked at ingredients already in use in cough and cold remedies in Canada, and these did include ephedrine and pseudoephedrine. The committee was therefore able to make recommendations regarding the appropriateness of these ingredients as OTCs for what specific indication and dosage. We therefore had a good basis upon which to assess the suitability of ephedra as an over-the-counter remedy.

In applying for premarket authorization for traditional herbal remedies, as for other drugs, the sponsor must identify the medicinal ingredient in the proposed product. In terms of traditional herbal remedies, if the product also contains some herbs as non-medicinal ingredients, these must also be declared qualitatively and quantitatively.

First of all, ephedra is a medicinal ingredient. Based on existing information, including the recommendations of our expert advisory committee on cough and cold preparations, ephedrine has been considered as safe and effective as an over-the-counter nasal decongestant at does of 6 to 8 mg per single dose repeated three to four times daily. As ephedrine is the major constituent of ephedra,

these same principles were applied for that substance as a traditional herbal remedy.

The labeling instructions applicable to preparations of ephedrine also apply to preparations containing ephedra. Cautionary statements regarding pre-existing conditions or potential interactions have been applied. We are unaware of any problems resulting from the use of ephedra preparations used according to recommended label directions.

What about ephedra as a non-medicinal ingredient? This is the area that gave us some difficulties a couple of years ago and where specific remedial action was required. Shortly after the introduction of our policy on traditional herbal remedies, we also had to issue a policy concerning herbs as non-medicinal ingredients. This followed the information letter of 1990. The policy states essentially that herbs may be used as non-medicinal ingredient in herbal preparations under the following conditions: No safety concern exists with the herb in question. Herbs that are proposed to be listed as adulterant in foods may not be used as non-medicinal ingredients, nor can those requiring cautionary statements when used as foods. No pharmacological action is exerted at the level used. To ensure that this criteria is met, a maximum of 10 percent of

the lowest documented therapeutic dose was set. This will become known as the 10 percent rule.

Like-acting herbs will be taken into consideration in calculating the no-pharmacological-action level. No herbs having the same effect as the medicinal ingredient may be used as a non-medicinal ingredient. And no therapeutic activity may be claimed or implied for the non-medicinal herbs. Under this policy, however, ephedra could be used at that time as a non-medicinal ingredient in herbal preparations.

What about ephedra as a food? Being familiar with this particular policy for the use of herbs as non-medicinal ingredients in drug products, the Food Directorate of our department adduced this criteria to provide advice concerning the acceptability of ephedra in foods, even though the rule had not been established for that purpose. This led to the marketing of preparations containing ephedra at 10 percent of the therapeutic dose that the lowest effective dose of ephedrine being 31 mg per day, the food products contain about 3.1 mg per day. These products were therefore sold without premarket authorization, as such authorization is not required for food products.

Subsequently, perhaps due to misuse or the fact that as a food the product did not contain any of the

warning statements present in drug labeling, and because consumers may have exceeded recommended usage directions, two serious adverse reactions were reported in 1993. Although as in most cases of adverse event reporting cause-and-effect relationship are not firmly established, a health hazard assessment conducted by our medical evaluators on the products involved in the adverse event reports determined that the products in question were likely to have pharmacological effect and have contributed to the adverse reaction. This assessment was conducted in January 1994.

In conclusion, it was therefore decided following this assessment that ephedra will no longer be permitted as a non-medicinal ingredient in traditional herbal remedies and that its use as food would also no longer be permitted. Therefore, the only avenue for marketing ephedra in Canada at this time is as a nasal decongestant, as a traditional herbal remedy, with the premarket approval requirement, and with appropriate labeling. Following that decision, the letters to trade were issued across the country and also to the industry association, and our field staff were advised that non-prescription products containing this ingredient as non-medicinal ingredients were to be removed from the market, as well as any other non-compliant products with the traditional herbal medicine policy.

Thank you very much.

DR. ASKEW: Thank you, Ms. Ho. We appreciate your sharing the Canadian experience with us.

Does anyone have any questions for her? Dr. Hui?

DR. HUI: I have been wrestling with this problem for a long, long time. I came to UCLA to study chemistry. Ephedra was one of the reasons why I came to the United States. It's very difficult to distinguish between what is a food and what is a drug. Think about glucose. Glucose is a drug when somebody is hypoglycemic, and glucose is a deadly poison for someone who is very hyperglycemic. And so it applies to milk. Milk can be very symptomatic for a lot of patients with lactose intolerance, but milk is also very useful for health maintenance, and also milk can be useful for someone to get some calcium. So it's very, very difficult for us to sort of define the way you are defining it.

Let's take a look at how the Chinese classified ephedra, ma huang, back in the first herbal. The Chinese classified the herbs into three major groups. The best are the ones that we can eat, that will be useful for health promotion. The worst are the group that will be used to treat diseases. Ma huang is in the middle. Ma huang is always used to treat diseases. It's not used as a food, so

I agree with you that it should not be classified as a food, and it should really be classified as something that will be used to treat symptoms and diseases.

Oftentimes, the Chinese use herbs in combination to minimize the side effects so that similarly toxic herbs can be used very safely and with very little side effects.

So I kind of find it difficult to hear all this today about how this should be--that there is no safe dose. In the wrong patient, there is no safe dose. It can lead to, you know, all kind of complications. And everything needs to be taken into consideration when we use anything that we put into our mouth, and that's why we need to train our professionals and also our citizens.

Thank you.

MS. HO: I do agree with you. I think one of the good examples is dextrose. And obviously these compounds are present in food, but if you think about a dextrose injection, there is no question that it is a drug. So I think that the intended purpose of the product is really a key in determining the classification of a product. I'm not sure that ephedra is ever used to provide nourishment, which you would expect from a food. I think that even when it is labeled as a food, it is--appears to be intended, anyway, for a therapeutic or medicinal purpose.

DR. ASKEW: Dr. Clydesdale has a question, and then Dr. Jasinski.

DR. CLYDESDALE: Could you just clarify? Did you say it was allowed under prescription and also as a traditional herbal medicine now?

MS. HO: It is not a prescription drug. It is allowed as a regular non-prescription drug as well as a traditional herbal medicine if labeled that way.

DR. CLYDESDALE: And could you explain how it's allowed as a traditional herbal medicine under your guidelines? I was just a little unclear.

MS. HO: It is allowed if labeled as a traditional herbal medicine.

DR. CLYDESDALE: Without any claim?

MS. HO: Yes. Also--no, no, not without claim. As a nasal decongestant with the dosage of 6 to 8 mg of ephedrine alkaloid three to four times a day maximum, and with appropriate cautions.

DR. ASKEW: Dr. Jasinski?

DR. JASINSKI: Yes, I was curious in your definition of lack of pharmacologic effect as being a defining factor. I have been drinking coffee, and I've got a tachycardia from drinking the coffee right now. So by your definition, coffee beans would not be allowed to be

marketed because you can get a pharmacologic effect from coffee beans. If you add peppers, i.e., you can take peppers, and I think taking the receptors, it's a pharmacologic effect, plus the fact that if you drink enough, you break out into a sweat, which is a pharmacologic effect. So I'm not sure how you define lack of pharmacologic effect.

The other thing is, in your conditions there, it would mean that people could not self-medicate themselves for osteoarthritis. You had arthritis listed, but I suspect a great deal of OTC medications and herbal medications are to treat osteoarthritis, which is not a self-limited condition by my definition.

I mean, I'm just looking at these as sort of being consistent, and I just--how you formulated your policy.

MS. HO: I'm not sure that patient can self-diagnose osteoarthritis. The condition is not permitted on OTC labels. However, the analgesics can be sold as a relief of pain due to arthritis. But you cannot have reference to treatment of the condition itself, only its symptoms.

DR. ASKEW: Dr. Ziment?

DR. ZIMENT: I have a lot of trouble with words, just as Dr. Jasinski does. For instance, I often think the word "traditional" where it is equivalent to the term

"modern antiques," because I don't know what traditional really means with these drugs. As far as I know, Dr. Hui, the Chinese never used to use ephedra for asthma until Drs. Chen and Schmidt showed that it was useful for this purpose. Similarly--

DR. HUI: That's not true, though.

DR. ZIMENT: Well, they used it for disease which was not called asthma, because--

DR. HUI: Bronchospasm and coughing.

DR. ZIMENT: Yes, but, again, the Chinese would use different terms. They wouldn't use the term "bronchospasm." Similarly, when you use ma huang or ephedra for nasal congestion, how do you know you're dealing with nasal congestion? Maybe it's a cold. Maybe it's a tumor. Maybe it's sinusitis.

Again, I don't see how patients can self-diagnose even nasal congestion any better than they can diagnose osteoarthritis, because there is always a differential diagnosis.

MS. HO: Some of the safety considerations in terms of non-prescription drugs include the fact that minor conditions or symptoms only can be mentioned on the label, also that the duration of treatment is usually limited to a few days and patients are advised to consult a physician if

they need to use the medication for a longer period.

With respect to the use of the term traditional, the reason we chose that term--and we just had to choose one, you know, and we debated between traditional, folkloric medicine--is that the policy was developed on the basis that we would accept references from the traditional literature as opposed to today's standard clinical studies. It was just a choice of term that we subsequently explained to the general public and to the industry.

DR. ASKEW: Mr. Guzewich?

MR. GUZEWICH: Ms. Ho, I'm very interested in the experience of Canada. I'm wondering if you are aware of experience with adverse events from ephedra or regulating ephedra in these kinds of contexts in other countries?

MS. HO: We had very few adverse effects in Canada. As I mentioned, there were two serious ones reported in 1993. But obviously the experiences in other countries did play a role in the decision to take action at the time. We had heard of a number of reactions in the United States as well as other countries. I don't have a breakdown of that at the moment, though.

MR. GUZEWICH: Are you aware of a situation in Europe or any other parts of the world?

MS. HO: Not specifically, no.

DR. ASKEW: We can open this up for questions of any of the previous two speakers in addition to Ms. Ho at this time. Dr. Ziment, you had a question?

DR. ZIMENT: Yes. I was rather interested in, glancing through the Ohio experience, Exhibit B. On page 19, the second paragraph, there is a statement from Dr. Varro Tyler, who is a great authority on herbal medicines, and he says, Recently--he's commenting on some authors who wrote recently as being shown that ephedra can cause weight loss. And Dr. Varro Tyler goes on to say: there is no substantial scientific information to support this statement; ephedra or its contained ephedrine is not an anorectic agent. And since we've been discussing a lot about the use of ephedra as an anorectic agent or as a weight loss agent, I'm rather interested in knowing what the proof is that it does have an effect when somebody as authoritative as Dr. Varro Tyler says it does not have an effect.

DR. ASKEW: Would anyone care to comment? I think in this nature people are responding to any type of thing that increases energy expenditure and energy metabolism as perhaps being effective against weight loss and is probably used in this context. But the documented clinical efficacy is something we want to address here.

DR. JASINSKI: I think there have been some publications, some clinical trials where ephedrine has been used to show that there's weight loss, which is not surprising. Its pharmacology is similar to amphetamines. If you take a large enough dose, you've got the same pharmacology, and its efficacy is going to be equivalent to amphetamine.

DR. ASKEW: Dr. Croom, could you comment on that?

DR. CROOM: Sure. I can't totally speak for Dr. Tyler, but let me say that in all probability what he is discussing there, it has not had a use in that. The studies mentioned in the Journal of Obesity are combinations of caffeine and ephedrine, the ones that I'm familiar with. And so I think he was probably at that time just stating that, yes, as you stated, it can raise metabolism but it is not typically used that way.

I think that's basically what he was trying to address, that it is not the typical use, it has not been shown that ma huang itself is used for weight loss and effective for weight loss, or ephedrine alkaloids in ma huang.

DR. ASKEW: Dr. Bruner?

DR. BRUNER: Well, in speaking about ephedrine used as an anorectic agent, there have been a number of

publications now. It's using ephedrine hydrochloride, usually in dosages of 20 mg on a TID basis in combination with caffeine, aspirin, and some theophylline preparations, in fact.

In the International Journal of Obesity, the February 1996 edition, Dr. Horton, who is in England, published a very nice study about postprandial thermogenesis using ephedrine, caffeine, and aspirin in the combination. And there are a number of publications by Dr. Astrup in Sweden, but it's ephedrine hydrochloride.

DR. ASKEW: Okay. Thank you.

DR. ZIMENT: One other comment on this. I may be wrong, but I believe that traditionally ma huang may have been considered to be a diuretic agent and also a so-called sudorific agent producing sweating. I wonder if there is any evidence that weight loss is just related to loss of free water.

DR. BRUNER: Well, there were some studies that were published a couple of years ago that looked at ephedrine hydrochloride causing fat loss versus muscle loss and preserving muscle integrity because of the adrenergic action, and it was felt because of the beta-3-agonist action that it induces thermogenesis.

DR. ASKEW: If we could try and stay focused on

the three presentations that we just had at this point in time, we'll have plenty of time for a more general discussion later. Is there anyone that has questions for the three previous speakers at this time? Yes, Dr. Marangell?

DR. MARANGELL: I'd like to request a written transcript of Dr. Ho's presentation. Is that possible?

[Inaudible comment.]

DR. MARANGELL: Thank you.

DR. ASKEW: Mr. Israelson?

MR. ISRAELSON: For Micheline Ho, is the milligram dosage calculated as ephedrine or total alkaloid 6 to 8 mg per day?

MS. HO: It's total alkaloids, ephedrine alkaloids.

DR. ASKEW: Thank you.

Dr. Wang?

DR. WANG: The same question I have also is weight loss products containing ephedrine alkaloids, is that regulated as a drug?

MS. HO: It would be considered a drug but a non-permitted drug at this time. It probably would have to go through the new drug route to get that product on the market.

DR. WANG: Also, another question for follow-up. When you did allow ephedrine alkaloid to be used as food, you stated that you used one-tenth of the drug maximum level, right? And that's about 3.1.

MS. HO: The lowest therapeutic dose, right.

DR. WANG: 3.1 mg per day. Is that a pure form of ephedrine alkaloid from ma huang stems ground up or is that a combination product that is allowed?

MS. HO: We're talking only products containing the equivalent of 3.1 mg of ephedrine alkaloid from herbal source.

DR. WANG: Herbal source--

MS. HO: Whether it be the ma huang the herb or an extract.

DR. WANG: Or extract.

DR. ASKEW: Yes, Dr. Ricaurte?

DR. RICAURTE: Dr. Ho, as I understand it, the Canadian Government and authorities have taken these actions in an effort to minimize adverse effects associated with the use of these products. One of the approaches you've taken is a pharmacologic approach about this issue of restricting the content to 10 percent of the effective dose.

My question is: What is to preclude an individual who either for--for whatever reasons is to misuse a product

from simply taking 10 times the recommended dose if it is just sold as a food product without any limit on the amount that can be purchased or how much can be used at a particular point in time?

MS. HO: Perhaps you misunderstood. Initially, ephedra was allowed with a 10 percent rule. Once we realized that because it was being misused, even at that 10 percent level it was having pharmacological effect, that's when the decision was made to no longer permit it at the 10 percent level or in food. So ephedra is no longer permitted under that rules.

DR. RICAURTE: Either as a food additive or supplement or as a drug?

MS. HO: It is permitted for sale as a drug, but not as a non-medicinal ingredient and not as a food.

DR. RICAURTE: I see.

DR. ASKEW: Dr. Chassy has a question.

DR. CHASSY: You seem to have set national policy in Canada, if I heard you correctly, on the basis of two serious cases, and this committee is being asked to address itself to the issue of association versus scientific evidence of causality that the ephedrine alkaloids cause serious consequences. Could you share with us those serious cases and how you reached the determination, which you

obviously did, that there was a causal relationship?

MS. HO: I don't have a lot of details about the two cases. I know that one was related to cardiovascular effect in a middle-aged male, I think, with a predisposing heart condition. The other one was a teenager who abused the drug product.

The decision was taken in the context not only of the Canadian situation, but also it was what was coming out of the United States and other countries. It was also taken because we knew that the products were being perhaps labeled as food, but they were being represented, perhaps orally, as medicative products. And they were recommended for weight loss, according to the information that we have. People were being told ignore label directions and, yes, do take ten tablets instead of two tablets today if you want the product to be effective or if you want to lose weight faster. And these were all factors that were considered in our decision.

DR. ASKEW: Dr. Benedict?

DR. BENEDICT: Thank you. If I understood the comment correctly from the Texas contingent, the majority of adverse reports in younger people were from OTC applications, and the majority of adverse effects from herbal products were in people over 30. And I'm wondering

if there is an elaboration of that statement and whether the Ohio contingent experienced a similar result.

DR. CULMO: Your understanding is correct. We have adverse events reported with the dietary supplement products in the younger persons, but the majority of those events are with persons middle-aged to older. And then the OTC products are the ones that created most of the adverse events in the younger persons.

DR. ASKEW: His question was whether Ohio had experienced that or not. Mr. Wickham?

MR. WICKHAM: Yes, that would be the same in Ohio, too--

DR. LARSEN: Would you use the microphone please.

MR. WICKHAM: Essentially that's the same that we found in Ohio. The young people, it was two OTC drugs with ephedrine and such, and the dietary supplements were generally the older, middle-aged women who were using them for dietary purposes.

DR. ASKEW: Yes, Dr. Croom? And then Dr. Dentali.

DR. CROOM: I want to ask Ms. Ho also a question. I want to make sure I'm clear. Could you explain that ma huang--what I'm hearing you say is you've had experience with safe use at 6 to 8 mg, and that is sold as a nasal decongestant, correct?

MS. HO: Yes.

DR. CROOM: And what kind of form? Is that a pill? Is that a spray? Does that matter?

MS. HO: They were oral use. I'm not familiar with any sprays at all, but they could be tablet or liquid extracts.

DR. CROOM: Okay. So in your experience, though, you're saying that this has happened enough that with an oral--I just want to make sure I know the limits here. And is it just ma huang or is it ever combined in other formulations?

MS. HO: We're talking about single ingredients. It's no combination with any other medicinal ingredients.

DR. CROOM: Thank you.

DR. ASKEW: Dr. Dentali?

DR. DENTAL: I have a question concerning the Texas experience. It appears that with this older age group, as it was called earlier, that the indications of use may have been weight loss in general. I am concerned maybe about the appropriateness of that. However, these are being marketed as dietary supplements, and I'm wondering if you did an actual analysis of the products associated with these adverse events and were able to determine which of them, in fact, were dietary supplements, meaning herb or herb

extract, and which were purified alkaloids. Do you have any idea of what might be the breakdown on that?

DR. CULMO: Some were analyzed, not all of them. And I don't--do you recall the breakdown?

Obviously, the first one we can think of is formula one.

DR. DENTALI: Was that an herbal--I mean extract or was that, you know, a mixture of alkaloids, or are we dealing with just one or two--or just?

DR. CULMO: It claimed to be ma huang extract, and actually, in the papers, it was admitted that synthetic was added.

DR. DENTALI: Again, this goes back to the distinction I wanted to make earlier. Quite possibly this is not a dietary supplement.

DR. CULMO: But it's labeled as such.

DR. DENTALI: I understand that.

DR. ASKEW: Further questions of the speakers? If not, I'd like to acknowledge that we've been joined at our table by the Commissioner of FDA, Dr. David Kessler.

Dr. Kessler, are there any comments that you would care to make at this point?

DR. KESSLER: Thank you very much.

DR. ASKEW: We have concluded our morning

deliberations at this point in time. We're going to break now for lunch. We will reconvene at 1:10, and we will start with Dr. Yetley giving us a focus on our charge.

[Laughter.]

[Whereupon, at 11:53 a.m., the committee was recessed, to reconvene at 1:10 p.m., this same day.]

AFTERNOON SESSION

[1:13 p.m.]

DR. ASKEW: While everybody is getting their seats, I just want to mention that this afternoon we will be getting the focus and charge for the committee from Dr. Yetley, and then we are going to have a market review and a safety evaluation by officials from the FDA. Then we will have later on the afternoon time for open public hearing for more comments from members of the audience that have approached the Chair and wish to make public comments.

Before we begin, we have a couple of administrative announcements from Dr. Larsen.

DR. LARSEN: First I have a question for Dr. Marangell. You asked about a transcript of Ms. Ho--it wasn't clear to me when you asked that question what particular transcript you were asking for, and we were trying to get the materials for you.

DR. MARANGELL: Of Ms. Ho's presentation.

DR. LARSEN: From the presentation.

DR. MARANGELL: We have summaries of all the others, but not hers, and there were several useful points that I would like to have available.

DR. LARSEN: Okay, yes. We did get the materials from her from her presentation. I thought it was some other

transcript you were looking for. So okay.

One of the folks that had registered for the open public hearing this morning that didn't respond when I first asked if he was here, someone told me that he had registered, is Mr. Christopher Grell here? I wanted to give him an opportunity to say whether he needed to--if he is here, whether he could wait until the 4:30 open public hearing or not.

[No response.]

DR. LARSEN: Okay. If not, we will just go on with the agenda as scheduled.

DR. ASKEW: Committee members that are returning to their seats now will find several handouts in front of them that you did not have when you broke for lunch, one of which is the charge and questions posed to the Food Advisory Committee and Special Working Group. You might want to get that out and follow along as Dr. Yetley gives us our charge. So we'll turn it back over to Dr. Yetley to give the committee their charge.

DR. YETLEY: This is fairly short, so maybe I'll just sit here.

I want to, before I start going through the pieces of paper you have in front of you, just give some general statements. I think that we have to make very clear what it

is that's on the table and what's not on the table. I alluded to it this morning, but let me come back to that.

What we're really asking the committee to look at is the scientific evidence or the scientific basis for coming up with a safe way of marketing dietary supplements which contain ephedrine alkaloids, or at least discussing the safety from a scientific perspective within the context of the marketed products. And we're not here to discuss what should be a drug or what should be a food. We're not here to discuss which dietary sources or which sources of ephedrine alkaloids are the best or the worst. We're not here to talk about whether or not the purported benefits or the claimed benefits have been proven or not. We're really talking about the marketed products, the products that are currently in the marketplace.

We have samples of them out there on the table in the back. You had in your handout the results of our market survey that indicated the label information and the ephedrine alkaloid content of these. Connie Hardy will be talking more about the market survey in a few minutes. So focus on those products. It's not about the drug products or other products. And it really is the science behind it and not the regulatory considerations.

Now, if you would turn to page 3 of your charge

and questions document, I think it would be easiest to start there. And in the middle of the page under the charge I think is what I just indicated, and that is that the purpose of this is to review the scientific data and other information related to adverse events associated with the use of dietary supplements containing ephedrine alkaloids and to provide expert advice on specific ways to address the public health concerns that have been associated with the use of these products. So it is a science discussion, and it is focused on dietary supplements.

We would ask that the committee first address the safety question from a perspective of can you identify a safe level of ephedrine alkaloids in dietary supplements for both the total ephedrine alkaloids that you find in the botanical sources, as well as ephedrine per se, and talk about that from both a per serving and a per day limit.

In doing that, what considerations are you taking into account when you think about margin of safety. How should we look at margin of safety in determining a safe level?

The third question we're going to ask is: Can you identify conditions of use for ephedrine alkaloids-containing dietary supplements under which there is no risk of significant harm? And we have suggested that the

definition of significant harm means are there a large number of adverse effects or a serious adverse effect in at least one individual.

The fourth question is: Can you identify conditions of use that are associated with a risk of significant harm, including levels and frequency of use above which there is a risk of significant harm? Using the same definition of significant harm. So we really want you first to focus on a safe level and the rationale that you have used to get there.

Assuming that after you give full consideration to this question and assuming that you come to the same conclusion that the working group did that there are probably safe conditions of use, then we will probably ask you to look at additional questions, such as those that would deal with how you would deal with a warning statement, how you would deal with the combinations with other ingredients that might be interactive in terms of their effects. But the first question is needed to deal with how do you define, can you define a safe level of ephedrine alkaloids in the types of products that are marketed as dietary supplements.

I think that concludes my remarks. We can come back to these with more discussion before you start your

full discussion in the morning. But I wanted to mention now because I think there are important aspects of the presentations this afternoon by Dr. Love and by Connie Hardy that will help you in making those decisions. So I wanted you to be sensitized to the question on the table.

DR. ASKEW: Thank you, Dr. Yetley.

Are there any questions of clarification at this point in time? Yes, Dr. Hsieh?

DR. HSIEH: I have a point of clarification. Are we here to address the ephedrine alkaloids in ma huang or address ma huang itself?

DR. YETLEY: The ephedrine alkaloids in the ma huang, unless you feel that they are so intertwined that you need to deal with them in a broader context. I think that's part of the science that comes to bear.

DR. HSIEH: Your statement is based on the assumption that all the effects that are shown by ma huang are totally due to ephedra alkaloids. Is that a good assumption?

DR. YETLEY: What we see that's common to the products--and, again, there will be more information in the presentations that follow. What is common in the products that are associated with the adverse events that we're talking about is the source of ephedrine alkaloids. I think

there is a legitimate scientific question as to whether or not those effects are due solely to the ephedrine alkaloids or whether other ingredients are also interacting with the ephedrine alkaloids to contribute to those effects.

DR. HSIEH: The reason I am asking this question is that ma huang is one of the oldest medicinal herbs in China, and it is very well established or we have documented that it is a very potent medicinal herb and it has many effects, whether adverse or medicinal, therapeutic effects. And I am not sure whether you can attribute all the effects to ephedrine alkaloids. So we have to clarify whether you want us to look at ma huang or to look at the ephedrine alkaloids in ma huang.

DR. YETLEY: We want you to look at the safety of these as they are marketed in the products that are now marketed as dietary supplements. So you need to put your knowledge of the traditional use, the chemistry and physiology and pharmacology that's associated with the traditional use, but you need to think about that in the context of these products being marketed as dietary supplements, products that are in the marketplace.

DR. ASKEW: Dr. Ziment?

DR. ZIMENT: Is there a concern that the safety of ma huang and ephedrine chain according to the accustoming of

the patient to the drug? In other words, the drug induces some degree of tachyphylaxis and, therefore, people tend to need either large doses of drug or it just loses effect? So should there be an initial dose and an adjustment dose?

DR. YETLEY: I think that's the kind of input that we're expecting from the Advisory Committee as you go through the issues. That would be one of the scientific components that's probably on the table.

DR. ASKEW: Yes, Mr. Israelson?

MR. ISRAELSON: With regard to Question 3 that the standard you are asking us to look at is significant harm, which has two sub-definitions, I'm just curious how you arrived at that definition, specifically in its two sub-parts, which is different from the statutory definition within the law. I'm just curious. Where do we need to go on this?

DR. YETLEY: We really wanted this to be a scientific issue. We assume that FDA, as it goes to implement whatever recommendations come out of an advisory committee, will deal with it in the legal context. But we wanted this to be put in a term that's more meaningful from a scientific perspective.

DR. ASKEW: Dr. Jasinski?

DR. JASINSKI: Just for clarification and to see

if my understanding is right, you cannot under the law--if this was a drug, you could require Phase I testing and safety data, which was traditional sort of safety data with the drug. This sort of exists in literature for ephedrine hydrochloride. To my knowledge, this doesn't exist for any of the herbal products, either in terms of a Phase 1 data with a standardized preparation or any sort of toxicity testing, you know, in terms of chronic administration.

My understanding is--the first question is you can't require this under the existing law.

DR. YETLEY: It's not required under the law.

DR. JASINSKI: Okay. The second issue which is here, the only way you can extrapolate from these questions would be going from the data on ephedrine hydrochloride where you can answer these questions in terms of level, to the ephedrine alkaloids. I really have two questions which I can't answer. One is: Is the alkaloids which exist as a base, what is their relationship to the ephedrine hydrochloride in terms of activity? And secondly is the question if you complex these, we already know if you put medications in a certain sort of matrix that's natural may alter this from--the pharmacology from the pure medication in terms of absorption and rate of limitation. And those are--if you have any information on this--I'm trying to

think and formulate a response to these questions, but those are the ones which I keep coming up with as sticking points which I can't answer.

DR. YETLEY: We are not aware of data on the botanicals that would answer the questions you have. There may be available--and one thing we would hope that if people have that type of data they would share it with us. But those are the scientific issues that we're asking this group of experts to discuss and to make some recommendations on.

DR. HUI: I'd like to respond to that. The Chinese actually have done a lot of studies looking at combination of herbs. If the proportion of the herbs are altered, actually pharmacological effects are altered. And I really think that this is a very germane question. We know that when you change sulfate to lactose, I think the dilantin level rises. So, I mean, we have that type of data even in pharmacology. So I don't think we can extrapolate from one to another.

DR. ASKEW: Yes?

DR. INCHIOSA: I think that some of these comments are really confounding it too much. The comments that you were making I think are germane to bioavailability, so it's true that the bioavailability absorption from the GI tract might be quite different in a mixture of different herbs.

The herbs themselves might contribute to affecting the alkalinity of the urine, which is going to affect the half-life of the drug, which is going to influence the steady state plasma concentrations. These things will have influences on bioavailability and actual half-lives of the drug. And I think once, whether it's administered as a chloride for reasons of compounding it, once the drug is in plasma, it's no longer necessarily the chloride salt. It is now the base in any salt that it--or any physiological circumstance that it's going to exist. So it's no longer ephedrine hydrochloride. It can be--

DR. JASINSKI: I don't disagree with you, but I at least would like to hear somebody talk about the chemistry and the science of this and how the alkaloids exist in the plants, what the potential chemicals are, what would particularly happen, whether, you know, in terms of--I don't even know what the PKA is of ephedrine in terms of its absorption when it hits the small intestine, whether if you take the extract--whether any of this is known.

DR. INCHIOSA: A great deal is known.

DR. JASINSKI: Well, that's what I'm asking for. I just don't have the background in my background to answer this question in terms of this, and I'm just wondering whether this data exists or it's been thought through.

DR. YETLEY: The information that we have was provided in the briefing book that was given out last October, which I think has been shared with a lot of the full committee. But it's also--again, we tried to bring in the experts and the types of expertise that would hopefully have answers or have information on some of these questions. I think they are very germane questions, and hopefully some of the experts around the table also can help with this discussion.

DR. ASKEW: Dr. Clydesdale?

DR. CLYDESDALE: At the risk of confusing this further, prior to these questions being answered, I think we would have to know as a committee if there were adequate analytical procedures for the compounds in question. And are there adequate analytical procedures not only for the pure compounds, but for the compounds as they exist within the matrix as it's sold on the market?

DR. YETLEY: Do you want discussion of that now, or do you want to defer it until after you've heard the presentations?

DR. CLYDESDALE: Well, it doesn't matter, but I think that prior to answering any of the other questions that we're asked, we have to have a way to analyze this, and with some degree of certainty and prior to even questioning

anything else that was asked. And I just wondered if that was available, and if that's going to be answered later, that would be fine. But I think it's the sort of foundation piece of knowledge that we must have.

DR. ASKEW: I think one of our pharmacognosists can answer that. Dr. Croom?

DR. CROOM: I want to let the people do their presentations instead of responding. I'll be glad to do that. What I want your guidance on, Dr. Yetley, is I think Question 3 is the thing to keep steadily in mind, and a little clarification, because I guess as a scientist, when someone says no risk, I can imagine a spill of this water on this microphone, and when I come to one serious adverse event and I get electrocuted. And so I think guidance on what are we doing to find a safe thing societally or however, just help us define that. Because no sounds more like why I go to church than a scientific analysis, okay? And I want to be very clear because this is a key point of where is the safety of public health, I think is what you're after here. But I think to hear the presentations is what I want the clarification for.

DR. YETLEY: I certainly think it would be useful as the discussion proceeds for people to indicate what they consider to be safe use and how individuals are defining it.

But you'll notice here that we did link the no risk to significant harm, not just to harm but to significant harm. And we tried to give some guidance in terms of significant harm could either refer to a large number of people would be adversely affected, or it could be an extremely serious adverse effect in one individual or a very few number of individuals. So that was our attempt.

I think if as you go through the discussion you feel that there is a different definition, then I think you need to clarify what definition you're using as you're presenting your perspectives.

DR. ASKEW: Are there any--yes, Dr. Fong?

DR. FONG: I Just wanted to answer one of the questions raised earlier as to how the ephedrine occur in plants. Alkaloids in general occur in plants in the form of a salt. It's not hydrochloride. Hydrochloric acid does not exist in plants.

Now, organic acids, a whole series of organic acids, so exactly how ephedrine occur and what organic acid it binds with, I can't tell you at the moment, but they do occur as organic salts. So the hydrochloride is a--in the purification process, hydrochloric acid is used as a very, very facile chemical.

DR. ASKEW: Thank you. Further comments or

questions of clarification of Dr. Yetley? Yes, Dr. Chassy?

DR. CHASSY: I know we've been over this before, but are we to consider a product that has ephedrine hydrochloride added to it as not germane to our discussion because it's disqualified by being mis-branded or mis-labeled?

DR. YETLEY: We're asking the question, regardless of source, is there a way to make dietary supplements containing ephedrine alkaloids safe for their intended use as dietary supplements.

DR. DENTALI: This begs the question, though. Is a product containing a purified, whatever the source of ephedrine and no other ephedra alkaloids, is that a dietary supplement? I feel it's important we understand that.

DR. ASKEW: Dr. Ziment--

DR. YETLEY: The issue of what's defined as a supplement or not as a supplement from a legal perspective I think is really outside the scope of this committee. But given the marketed products, what are the conditions for safe use? Are there conditions for safe use?

DR. DENTALI: So for purposes of the committee, we may and shall consider any product containing ephedrine alkaloids marketed as a dietary supplement as a dietary supplement in our scientific review of the information. Is

that correct?

DR. YETLEY: Part of the scientific review. And if there's evidence that one form or another form is safer, then that's a legitimate scientific point to be made.

DR. DENTALI: I'd like to respond to that. There's very little information on that. I did happen to come across two studies, and I can get the reference to you and possibly a copy of it. One was conducted in Japan. They had been seeing--they reported seeing a high incidence of adverse effects recently with products containing ephedrine alkaloids. They realized that their data was based on ephedrine and not the extract, and they conducted an animal trial with equivalent amounts of ephedrine alkaloids and comparing the two--in mice, I believe. I'd have to check the reference. Generally, they found that absorption levels were about half time-wise and the concentrations in the plasma were about half.

DR. YETLEY: I think that's important to share with the committee when you get to that discussion point.

DR. ASKEW: Dr. Ziment and then Dr. Marangell.

DR. ZIMENT: I think there's one problem with two cultures. We're the scientists trying to get reasonable information, and yet the patients who are taking herbal medicines rather than the standard drug produced by an

ethical pharmaceutical firm, that individual is looking for magic. And if somebody's looking for magic, they're not going to be bound down by scientific recommendations. So even if we limit the amount of ephedra alkaloids in the drug, a person who's looking for a particular effect is simply going to take enough of the drug to give them that effect.

I think we're really expecting some sort of scientific control over the way people exercise free behavior, and that's not going to be easy.

DR. YETLEY: We didn't say it's going to be easy.

DR. ASKEW: Yes, Dr. Marangell?

DR. MARANGELL: I understand that you're saying our charge is not to look at whether or not this should be considered a food or a drug, but I have difficulty divorcing these issues. I'm willing to look at a drug that has some side effects and risks in certain populations versus the benefit as a physician. When I'm looking at these and we're talking about bioavailability and what matrix and what's a safe level, that sounds an awful lot like a drug to me. And if you're asking us what's safe if this is going to be a food, when I think of a food I think of grapes that you can have as much as you want and you're not going to risk these types of adverse events.

DR. YETLEY: Think of the products that we have back there on the table. That's what we're focusing on, that type of product.

DR. MARANGELL: But whether or not that should be subjected to the same criteria as you would for a drug if it's being used and marketed as a drug, even though it's being called a dietary supplement?

DR. YETLEY: Not so much the regulatory standards or the regulatory hoops that they need to go through, but are there conditions, based on the best to your knowledge, that would allow us to have these products marketed safely as dietary supplements.

DR. MARANGELL: Okay. And one option would be that there is not a level?

DR. YETLEY: That's an option.

DR. MARANGELL: Okay. Thank you.

DR. ASKEW: Yes, Dr. Georgitis?

DR. GEORGITIS: One other question I have to ask that fits the charge and representing--being a pediatrician, is the abuse potential, is that something we should be covering as part of this discussion?

DR. YETLEY: Certainly if abuse is a possibility, the question would be: Are there ways to minimize or prevent that?

DR. GEORGITIS: Thank you.

DR. ASKEW: Other questions of clarification? Yes, Dr. Clydesdale?

DR. CLYDESDALE: I'm sorry to raise this, but, you know, part of the reason there would be abuse of such products, as I look at the ones in the back, is because of the claims that are made. The type of claims are exactly the claims that lead to abuse. Obesity, I mean, that's the kind of claim that would lead to abuse. And although we're not discussing claims, the question was raised about abuse, and that's tied in my mind directly to the type of claim that's made. A broad-range claim like prevents obesity is going to lead to abuse.

DR. YETLEY: Well, again, the first consideration is: Is there a safe level? And how do you arrive at that? If you reach the decision, if you agree with what the working group said earlier that there are safe conditions of use, then the next question will be: What kinds of information should be on the label to ensure that safe conditions of use are likely met or likely followed?

DR. ZIMENT: The problem, of course, is that we might say safe, but we're not saying it's effective. And at that point, people are going to take a dose that will be effective, and then it won't be safe.

DR. YETLEY: We're really focusing on safety.

DR. ASKEW: Dr. Kessler?

DR. KESSLER: Let me try to bring a little clarity, if that's possible, because I'm the one who asked for this meeting.

I've become aware over the last several months of two deaths of two young, healthy individuals, one in Florida and one in Boston. Dr. Love will talk about many more adverse events, but I've looked pretty carefully into the facts of those two tragedies.

What we need help with--we need your scientific advice--is how to reduce those very significant risks, as well as other risks that have been associated with these compounds. That's what we need help on. We have the best food and drug lawyers. With due respect, I understand the need to understand the standards and the drugs and under foods. This is a scientific meeting. We have to make sure that we have fulfilled our responsibility. We can't prevent all risk. We're not talking about dropping a glass of water, your analogy.

We have two very real cases that the medical examiners have at least associated with the use of the products, the compounds under discussion. We need to reduce those risks. You're never going to reduce it to zero.

You're never going to have somebody not do something very stupid that you can't predict. You can't safeguard against everything in this world. But I am convinced that those two individuals died needlessly because the information wasn't communicated to them about the hazards associated with these products.

That's the job of this committee, the scientific discussion, how do we reduce those risks. Everything else we will handle. We will deal with the regulatory issues, with the legal standards. In the end, this is about safety and safety that has real effects on real people. That's what we have to reduce. We've got to make sure, in my view, that we fulfill our responsibilities so that we can reduce the harm that we've seen, certainly most recently.

DR. ASKEW: Yes, Dr. Hsieh?

DR. HSIEH: This will come back to my question again. Do you want us to look at the compounds, or do you want us to look at the herb? And the two should not be equated.

DR. KESSLER: I'll let Dr. Yetley and Dr. Love answer that question.

DR. YETLEY: I understand that the two are not equated, but both could be ingredients in the products that we're seeing. So you need--the botanical is certainly very

common, or at least extracts of the botanical, concentrated extracts of the botanical are very common in these products. But it is also possible that some of these products may have synthetic form, so it's really both.

DR. ASKEW: Dr. Jasinski?

DR. JASINSKI: From another context, I've been thinking about this question because I've been--it's interesting, the cyclical theory of history has been that we're getting to the forefront of stimulants again, and we had this whole class of drugs we call stimulants, which range from caffeine to cocaine to the amphetamines, some other drugs, and the question of what is a safe level of stimulant sort of action, you know, that we can tolerate and which is particularly safe. And the only consensus I can--because it has been over some questions over, for example, caffeine, which is what levels of caffeine can we tolerate, because there is caffeinism and there is concern about adding caffeine to products and using this as a medication. But the only consensus I can see is that people will tolerate the level of activity of what would be the average daily consumption of coffee, which is about 260 mg of caffeine a day. So if you ask what a safe level would be, it would be those levels of ephedrine which would be pharmacologically equivalent in stimulant action to that

produced by coffee. I mean, that would be one position to take in terms of doing it.

You could probably extrapolate from existing data in terms of the ephedrine hydrochloride and make some guesses of what that sort of level would be, but that would be one approach. That's the only thing, sitting here, you know, thinking--trying to think deep thoughts through this, because I struggle with this with some of the other sorts of stimulant agents. But that to me would be one starting level.

DR. ASKEW: We had two quick questions, Dr. Inchiosa and then Dr. Ziment, and then we'll go into our presentations and perhaps that will help you somewhat, and then we'll have more time for discussion.

DR. INCHIOSA: Dr. Jasinski, caffeine and ephedrine, though, are not equivalent drugs. You're just looking at the central nervous system, the fact that they both are central nervous system stimulants, and you could characterize or equate them in terms of that effect, but ephedrine has many other peripheral effects which are the basis for a good deal of its toxicity. It's arrhythmigenic in a special way because of its beta activity. It blocks uptake of catecholamines. It interferes with metabolism of catecholamines, can cause myocardial necrosis. So it has

many other effects. You can't just take one property and use that as a standard for deciding a safe dose.

DR. JASINSKI: But it's a starting point. The only thing is if you talk about people taking it for its psychoactive effects, the question is you could predict what would be equal psychoactive effects or level of psychoactivity, which is going to be relatively low doses of ephedrine. And we've heard that the adverse events were dose-related, and I suspect that the levels that we're going to come up with, if you compare it to, say, average levels of caffeine, the dose of ephedrine is going to be relatively minuscule compared to existing doses.

DR. INCHIOSA: But I don't think you can deduce from that or conclude from that that would be a safe dose of ephedrine, because at that equipotent central nervous system effect, you can have, as I said, many of these other effects, which are much more serious.

DR. JASINSKI: I don't disagree with you, and this is frustrating because if you're trained as a scientist generating data, serious effects come up with, what, one in 100,000, one in 200,000. I've heard no data predicting the level of this.

I listen to my colleagues at the FDA and the statisticians talking about, you know, predicting rare

events and how many patients you have to examine in a clinical trial to be assured you're not going to get a one in 100,000 event or one in a million event, and all of this sort of data in these discussions, the sort of data I'm used to. Listening to this with tabulating cases and, yes, we have some serious events, but--I mean, we have a numerator but no denominator in any of this, and coming back to predict safety data, they're asking us to predict safety data without telling people to go out and do a clinical trial to validate the predictions.

DR. ASKEW: Dr. Kessler?

DR. KESSLER: Welcome to the world we live in.

DR. JASINSKI: I know.

DR. KESSLER: I understand the angst. I understand the frustration. But that kind of data, the things you want, may not be readily apparent. What I ask you to consider is to give us your best judgment in light of what exists. We're not going to be able to have all the data that one would want in the world of clinical trials. But there is reason, in light of what we've seen for us to do a better job with regard to these products. There are unknowns. I understand the angst. We understand the limitations. You can put all the caveats that you want. The one choice that we really don't have is just to throw up

our hands and say, gee, you know, we can't try here.

DR. JASINSKI: I agree with you. I'm not disagreeing with you. That was not my point. I'm just saying this is not what we have in this case, and I'm sympathetic to the FDA given the law and given the issues. You have these issues, and what you can project from this as scientific data is relatively little. And I was only suggesting, I was responding to this, we're not going to get this sort of data because they're not able to demand these sorts of clinical trials. So we're never going to have this.

That's why I'm saying if you're going to pull something out of your hat, you pull a level of stimulant activity that's tolerated by society and it can be defended. And that was juts a suggestion to start there.

DR. ASKEW: Well, I think that, Dr. Jasinski, if you work on the caffeine-equivalent theory for the next ten years and come back and give us a standardized format, that might work. But it won't right now.

We need to get on into our presentations here, but we've got a couple of people that have questions. I don't want to cut people off. Make it quick. Dr. Ziment?

DR. ZIMENT: As somebody who has been treating asthma for a long time, I regard ephedrine as an asthma

drug. And I think I know that the dose is something between 50 and 60 mg three or four times a day. And I rarely have changed those dosages in treating patients, whatever their underlying or secondary condition may be. So I think we should use those dosages as a starting dose of what is safe and reasonable, and make the equivalent dose of ma huang equated to those dosages of pure ephedrine.

DR. ASKEW: I think this is helpful, and I think this is what the committee is being asked to do with the expertise that is here to have a discussion on this, and we'll get into this further discussion tomorrow.

Someone down at the end. Dr. Ford, you had a question.

MR. FORD: Yes, and it's Mr. Ford. I just wanted to address, Dr. Kessler, one thing that you said about the angst. There is a lot of angst, and I know well that you understand it. But you need to understand also that one of the components of the angst is that ten months ago this group was pulled together, the advisory group, and I think we carried out our charge very well. And here, lo these ten months later, our recommendation has not been put into force. There have been two tragedies in the intervening time. I don't think the data that are being presented are any different terribly from the data that we had--and the

character of the data than we had ten months ago. And I think there's angst, at least over at this part of the table: Are we going to get a decision out of the agency based on the information available but also the feedback from the expert panel that you pulled together?

DR. KESSLER: We will make a decision based on the record, which includes all the scientific data as well as the advice of the advisory committees.

DR. ASKEW: We're not starting from ground zero here. We had a report from the committee when we began this, and the discussion that went on and the dose levels that were discussed at that committee meeting are certainly relevant. That will be the starting point for our further discussion here.

This committee is the full committee, and the working group committee was not charged with making a decision for the full committee. So it's now up for-- sometimes when these things have to be re-discussed again, it does seem like you're starting from ground zero, and I understand your frustration.

Let's go into our presentation here. The first one is from FDA, Ms. Constance Hardy, who is going to talk about the second market review with regard to the ephedra alkaloids.

MS. HARDY: Good afternoon. I will be discussing the market review of ephedrine alkaloid-containing dietary supplements. I think everybody has a copy of the most recent updated chart review. You should have been given that this morning, so if any of you received anything in the mail, that has been updated. You also should have a copy of each of these slides that have been passed out to you if you cannot see something.

As you may remember, during the summer of 1995, the Food and Drug Administration conducted a market review of dietary supplement products that contained a source of ephedrine alkaloids. That review, which consisted of approximately 100 products, was basically a snapshot picture of the marketplace. We collected information on the labels of the products, including product ingredients, directions for use, warning statements, claims, and analytical values. For purposes of the market review, we classified products into three major categories: weight loss, energy producing, or ergogenic/body building (performance enhancing). It should be noted that these categories are not mutually exclusive because in some cases products may have both energy and weight loss claims on the label.

In the market review of 1995, we selected only a few products that were promoted as street drug alternatives,

i.e., those which are marketed for mind- or mood-altering and stimulant recreational drugs. The paucity of data available on the latter products may have been due in part to the types of establishments from which products were purchased. Establishments sampled during the 1995 review consisted primarily of health food stores and mail order firms which predominantly sold ephedrine alkaloid-containing products for weight loss, energy, or ergogenic or performance enhancement purposes. Street drug alternatives were not normally sold by these sources, and the number of street drug alternatives was not evident to the agency at the time.

Since the 1995 review, the agency became aware of the death of a 20-year-old college student who died from the use of an ephedrine-containing dietary supplement represented as an alternative to a recreational street drug. Subsequent to that, FDA identified a number of alternative street drug products marketed on the Internet as well as in certain retail establishments and magazines targeted to persons seeking alternative recreational drug sources. These products often use phrases or names that are frequently associated with street drugs. In some cases, products are marketed with claims concerning special activity or erotic sensations.

In particular, some dietary supplement products are marketed as a substitute for MDMA (4-methyl-2, dimethoxyamphetamine), a methamphetamine analogue. The substance is popular among college students and young professionals and is also known as "ecstasy," "XTC," "Adam," and "X." The precursor of MDMA is MDA, which is 3,4 methylene dioxyamphetamine), an amphetamine whose use results in destruction of serotonin-producing neurons which play a direct role in regulating aggression, mood, sexual activity, and tolerance to pain.

In small doses, MDMA affects mood and behavior by acting as a mild intoxicant. The user is reported to experience mental clarity and enhanced alertness, positive feelings and attitudes towards others and himself, feelings of warmth and love, a greater ease in accepting positive and negative expressions, and positive feelings and attitudes towards others and himself. Many street drug alternative products highlight these effects in their labeling, as you can see on the slide there. For example, the following claims were noted on the label of several products: "love and light," "euphoric pleasure," "ecstacy"--spelled deliberately wrong--"delight that arrests the body, mind, and soul," and "elevate your mood" and "visionary vibrations."

Because of the increase in the number of adverse event reports involving ephedrine alkaloid-containing dietary supplements and an increased awareness of street drug alternatives, a second market review was conducted, beginning in April of 1996, with an emphasis on those drugs considered to be--excuse me, on those products considered to be street drug alternatives.

Combining the results of the two market reviews, approximately 125 different dietary supplement products containing ephedrine alkaloids were collected and evaluated. Some products collected for the second market review were duplicates of those obtained for the first market review and are noted as such on the chart that was provided to you. A duplicate is a product which has the same ingredients as a product with the same name and manufacturer or distributor. It is not necessarily the same formulation. Duplicate sampling was the result of the random collection methods employed as there were no deliberate attempts to duplicate any product sample.

Is that focused? I can't see it from here. I guess you can read your handout. It's hard to read the writing on the bottom up here.

Let's look at some of the findings of the reviews. Evaluation of the product labels and labeling revealed the

following major types of claims. The numbers that are up there--I don't know if you can read them--refer to the number of products out of 125 that had specific energy claims; you'll note that 68 had that; weight loss, there were 47 in that group; body building or ergogenic was 33; asthma and allergy, 4; euphoria was 8; and there were eight products which had o claims at all. In many cases, products had more than one type of claim.

Here are some of the types of claims noted in the market reviews. One of the other types of claims which was not addressed in the previous chart is the use of the words "natural" or "100 percent natural," and in one case the combination of the words "natural" and "safe." The majority of street drug alternative products used such terms, but to a lesser extent, the same terms were also found in the weight loss, energizer, and ergogenic categories. Many proponents of dietary supplement products highlight by using bold print or color contrast to emphasize the "naturalness" of a product.

The common denominator linking products contained in the two market reviews was a source of ephedrine alkaloids as indicated on the labels. Product labels, however, did not necessarily specify the form of the botanical source of ephedrine alkaloids, that is, whether it

was an extract, a concentrate, or raw herb. Here are a few examples noted in the ingredient statements.

In some cases where the ingredient was listed as ma huang or ephedra without any further clarifying terms such as an extract or a concentrate, the ephedrine analytical values found on the products were higher than could be expected for the range of ephedrine alkaloids known to be present in the natural herb. It should also be noted that Sida cordifolia is another botanical source of ephedrine alkaloids.

I did want to point out that if you look at this slide, we are aware that ephedrine concentrates of the products that I looked at and the agency looked at, we have seen a 6 percent concentrate, an 8 percent, a 12 percent. You can see that one of the companies puts up there standardized for 6 percent ephedrine, the third one down; whereas, if you look at the next to the last one, it says standardized for 6 percent ephedra, whatever that means. The term GPH, we're not sure what that means. But basically this is a smattering of what we see out there.

This chart breaks down ephedrine alkaloid levels per serving into increments of 5 mg. The first column that you see on that chart would be anything that would be below 1 mg. So it's basically 0 mg detected. From that point on,

each of your columns is in increments of five, such as 1-5, 6-10, et cetera.

Total ephedrine alkaloid levels range from not detected to approximately 110--that was the highest reading that we had--per serving. The median range for all products is approximately 17 mg per serving. You should note that the median range of ephedrine alkaloids for street drug alternative products is very close to other ephedrine alkaloid-containing dietary supplement products marketed for energy, weight loss, or as ergogenic aids. An item of note is that the current method of analysis used by the agency detected low levels of ephedrine alkaloids in some of the ergogenic products and possibly under-reported those levels. At this time the agency is concerned that this may be a methodological artifact due to the protein matrix of the products which interferes with recovery of the ephedrine alkaloids. The agency is currently developing a specific method to overcome this problem.

Although a source of ephedrine alkaloids is the common substance noted on the labels of each of the products reviewed, most products contained other possible "active" ingredients noted on the label. For this particular review, an active ingredient is defined as a substance other than water, binders, fillers, flavors, and colors. In looking at

this slide, please note the numbers above the top of the columns--I don't know if you can see that up there, but on your handout you can--refer to the total number of products which had a specific number of ingredients which are noted on the horizontal axis of the chart. You can see that there were eight products with 1-2 ingredients, 28 with 3-5, et cetera.

I also want to point out on that chart, although it's not up there, we did have a couple products that really have a very large number of ingredients, particularly in the ergogenic area, some as many as 61 ingredients in one product.

The agency is concerned that the likelihood of adverse events may be increased when some other substances are combined with ephedrine alkaloids. Many substances are known to or suspected to have physiological or pharmacological effects that may increase the risk of adverse events when combined with ephedrine alkaloids. For example, substances that may affect renal function or clearance--that is, salicin sources and amino acids--those that have stimulate effects--that is, caffeine sources--diuretic effects--that is, Uva ursi--stimulate laxative effects--that is, senna or cascara--or other interactive effects--that is, something such as yohimbe.

You can see by this chart the number of products which contained the various substances which I have discussed. Some of the more common active ingredients found within the 125 products were those which contained a caffeine source--that would be something such as kola nut, guarana, green tea, yerba mate--a salicin source, which would have been noted on the label, something such as white willow bark; nutrients, those being vitamins and minerals other than chromium; amino acids; stimulant laxative, something such as cascara sagrada; herbal diuretics other than a caffeine source--we counted uva ursi, licorice and smilax; also glandulars, RNA/DNA, and chromium was in a category by itself. Glandular, amino acids, and RNA/DNA ingredients were frequently found in the ergogenic category of products.

Let me talk a little bit more about a few substances included in the categories on this slide. In particular, caffeine is a central nervous system stimulant that can induce nervousness, insomnia, and tachycardia. Various sources of the substance which were noted in the market reviews were the green tea, Camellia sensis, guarana, yerba mate or Ilex paraguariensis, and kola nut. The combination of caffeine and a source of ephedrine alkaloids was noted in the majority of products contained in both

market reviews.

Uva ursi, which is also known as bearberry, is an example of an herbal diuretic contained in many ephedrine alkaloid products. The compounds ursolic acid and isoquerceetin are mild diuretics. The leaves of the plant contain the glycosides arbutin and methylarbutin which are purported to have antiseptic activity.

Senna, or Cassia acutifolia, and cascara rhamnus, which is also known as Rhamnus purshiana, are both examples of potent stimulant laxatives.

I would like now to switch and talk about warning labels. Warning labels for ephedrine alkaloid-containing dietary supplements are either non-existent or have several specific elements. The elements can be categorized as follows: disease or condition states, drug interactions, potential adverse effects, age restrictions, maximum daily use imperatives, or in some cases a very general statement. Of the product reviewed, the number of products that had each of the aforementioned elements were as follows: 26 products had no warning statements at all; a general statement was noted on 14; disease or condition states were on 86 of the products; drug interaction statements were on 37; adverse effects noted were on 25 products; maximum daily use imperative--that's something to the effect "Do not

exceed"--you know, it specifically has the word "exceed." That was on 35 of the products, and age restrictions was 35.

An example of a general warning statement was something such as "Please consult your physician before beginning any nutritional or exercise program." Disease or conditions which were noted were such things as high blood pressure, diabetes, and pregnancy. Specific drug interaction warning statements often refer to MAO inhibitor drugs. Adverse effects noted in the warning statements were terms such as nervousness or sleeplessness. Age restriction statements noted referred to children under 12 or over the age of 18.

In closing, I would like to emphasize that a comparison of street drug alternatives to the ergogenic or weight loss/energy type of products reveals that they are very similar with respect to the types of ingredients and the ranges of ephedrine alkaloids. Street drug alternative products in general do not have significantly higher levels of ephedrine alkaloids as compared to other products. You have seen that the median range of ephedrine alkaloids per serving is approximately 17 mg, and a similar level range is seen in the street drug alternative products. With respect to the actual declaration of the source of the ephedrine alkaloids, you have seen that many of the ingredient

statements were variable and at times confusing. As far as active ingredients, we noted that the majority of products contained 11 to 20 active ingredients, with the greatest number of ingredients being 61. In addition, many of the products had ingredients which contained substances known to have specific physiological and/or pharmacological activity. With respect to the warning statements we noted the elements of the statements varied greatly in the content as well as the information provided. The main issue of concern with ephedrine alkaloid-containing dietary supplement products, regardless of the claims and/or images on their labels, is the presence of ephedrine alkaloids. It is clear that the common link between the ephedrine alkaloid-containing products is the presence of pharmacologically active stimulants--the ephedrine alkaloids.

Does anybody have any questions?

DR. ASKEW: Thank you for that second market review, Ms. Hardy.

Does anyone have any questions? Dr. Marangell?

DR. MARANGELL: Could you comment more on the assay that you used and by what percentage do you think it might underestimate ephedrine levels? And did what you found at the FDA correlate with what is on the labeling of the products?

MS. HARDY: I'm going to defer that to Dr. Bill Obermeyer, who is the chemist who helped develop that method.

DR. ASKEW: Dr. Obermeyer is a chemist with FDA who is coming up to comment, respond to the question.

DR. OBERMEYER: The assay they were using, one of the products--actually, two, have high amounts of protein in it, and the extraction appears to be very low when we do the analysis, but when we come and do the spike recovery to check our efficiencies for recoveries for this specific product, we also get a very, very low recovery. We're working on this one, and we have reported the values for this product.

Did that answer your question? Or could you repeat it more specifically?

DR. ASKEW: Go ahead and try it, Dr. Georgitis.

DR. GEORGITIS: Would you tell us what your lower level of sensitivity is? And could you tell us in terms of your recovery rate, when you spiked the sample, what percentage of your spiked sample do you actually recover in your assay?

DR. OBERMEYER: We have a wide variety of matrices to deal with. In general, we are recovering with the various alkaloids, the six alkaloids, approximately 80

percent of our spike recovery. We also use an internal standard, phentermine(?), which extracts the same efficiency as ephedrine and pseudoephedrine, to also check for a matrix effect.

Our lowest sensitivity for this assay, on our analytical we use it as mg/gm. It is a 0.25 mg/gm level.

DR. ASKEW: We have further questions of a technical nature for Dr. Obermeyer while he is up here. Yes, Dr. Croom, and then Dr. Hui.

DR. CROOM: I'm not sure, Bill. Are you all going to present more of the analytical data? Or is this our only chance to talk to you about this? I'd like your recommendation. If there were dose limits set, which is one of the questions, with the currently available analytical methods what would you see is reasonable for variation that you would expect? And as you've pointed out, these aren't methods developed for just one product matrix, and so any other recommendations you would have to say, I would like, that, you know, you think would make this a doable method. If we say there is an amount of alkaloids, what do we need, what do we already have to make that realistic?

DR. OBERMEYER: That's a very good question. I think in a serving size we can safely do approximately 5 mg of total alkaloids per capsule or tablet or, you know--I

guess the serving size is approximately three-quarters of a gram, somewhere average in that range. That would be sufficient for a good analysis at this time.

DR. CROOM: All right. Let me give you a hypothetical then. Let's say, just to make the number easy, let's say it was 10 mg and we said but we don't want it to vary so much. But if the analytical method has some 20 percent variation or 25, so in other words, you don't want to set a standard or a level that's not doable. And I would appreciate it, actually, if you had other recommendations on what it would take, with obviously so many complex products, to make this a real thing, Bill, and not just a piece of paper.

DR. OBERMEYER: Right. Again, it's very difficult for me to describe the matrix effects that we've seen in the different products. And looking at some of the industry's assays, they specifically state that they will only use that method for their products. We have, like I say, a wide variety of matrices, and extraction efficiencies are different for a lot of them. So a ballpark figure for the analysis, which appears to work for a relatively high number of products, would probably be in that 5 mg range.

DR. CROOM: Okay. I want to make sure I'm clear. If I say 10 mg is a safe dose, does that mean the analytical

method would only tell me between 5 and 15 I've got a variation there? What's my variation at that level?

DR. OBERMEYER: The variation, we'll still working on the validation for accuracy, precision, reproduceability to get those numbers very similar to what a pharmaceutical company would be, to be able to report those in a very accurate way.

DR. ASKEW: Dr. Hui, and then Dr. Clydesdale.

DR. HUI: Under the area on ingredients with suspected physiological and pharmacological activity, how do you--

DR. LARSEN: Please use the microphone so we can--

DR. HUI: I'm sorry. Under ingredients with suspected physiological or pharmacological activity, is this based on chemical determination or is it based on pharmacological studies? Are these adulterated compounds or what?

DR. YETLEY: That is not a specific relative to those products. That is a--we need Dr. Love here to help answer that, but that really was an issue that we were raising for discussion by this committee: Are these other ingredients that we are commonly seeing in these products contributing interactively or in some way to an increased risk? And that is the question, and it's a very open

question, and I don't think we meant it to be anything more than that.

DR. ASKEW: Okay. We'll get to you, Dr. Jasinski. Dr. Clydesdale next--

DR. JASINSKI: Just a question of Dr. Obermeyer. What is the extraction efficiency? Have you done this? If you take the herb and you make a tea, what is the extraction efficacy?

DR. OBERMEYER: We did that for the last market review, and that one we had to partition it. We partitioned it as the classic chloroform extraction. Again, we were running probably--

DR. JASINSKI: I'm not talking about your chemical analysis. If somebody makes a tea, what is the extraction efficacy? I mean, that's--

DR. OBERMEYER: That depends on brew time. So if you would steep it for one minute versus three minutes versus someone that forgot it in their tea cup for ten minutes, that would be much different.

DR. JASINSKI: Well, what's the worst case? What's the maximum extraction efficacy you can do if you make a tea and you put it in the pot and you boil it up?

DR. OBERMEYER: We have not worked on that for the maximum. What we would extract it for would be methanol to

be the maximum out of an herb, which would be--

DR. JASINSKI: I mean, the question before the group is, you know, in terms of dose and what you're going to get and what the safe dose is going to be. If you don't know what people get out of the herb when they brew it, there's no way to answer this question.

DR. OBERMEYER: Right. Most of the products really are encapsulated or tablets of the ma huang extract. This is what we are seeing mostly. And very few products are actually the herb root as a tea.

DR. CROOM: Let me respond on some of that. The values that we're seeing is what is in the plant material, and that's the way we're talking about having a standard. In other words, what is extracted is going to be less. That's very different. In other words, we're setting a maximum, if you set a maximum number. If you took ephedrine hydrochloride, you've got 100 percent of that bioavailable, supposedly. No doubt, whether it is in the crude herb or how you brew it--and, by the way, the Chinese brewing is 20 minutes; it's not five minutes as a tea. And so when you prepare it, it's going to be less. So my point is if we're interested in trying to find out the level of alkaloids, the level that you're saying you're comfortable with, Bill, in your analyses, is certainly what's there, not necessarily

what is extractable, which should be lower. Is that not accurate?

DR. OBERMEYER: That's correct.

DR. CROOM: If we set legal regulations on the amount. So this is another safety margin that we're going to be--whatever level we set is theoretically extractable, not a hundred percent extractable.

DR. ASKEW: We have several people waiting to ask questions here. We'll go to Dr. Clydesdale next, and then Dr. Dentali, and then Dr. Hsieh.

DR. CLYDESDALE: On the matrix effect that you get with protein--is that on? If you're able to overcome that, what happens if the protein sources change in preparing the capsule, if you go from, say, casein to soy protein or something?

DR. OBERMEYER: We haven't work on all the different types of proteins yet. We're actually working on several specific products that are just protein formulations with caffeine sources and ephedra extracts added to them.

DR. CLYDESDALE: Would you guess that there might be differences for each protein source?

DR. OBERMEYER: With the trouble we're having, we hope not.

DR. ASKEW: Dr. Dentali?

DR. DENTALI: It's my understanding that a method has been submitted for the AOAC peer review process. Is that the same methodology that you're talking about that you are using?

DR. OBERMEYER: For the general product review, yes. The other ones containing the high protein content will be slightly revised from that, yes.

DR. ASKEW: Dr. Hsieh?

DR. HSIEH: Does your analytical method take into account the conjugated form of the alkaloids? Are the alkaloids present in appreciable amount as conjugated forms?

DR. OBERMEYER: In the extraction, we are hopefully removing the conjugation and we then use the solid-phase extraction to clean it up and then analyze for the free base.

DR. HSIEH: You said "hopefully." That's not good enough.

DR. OBERMEYER: Well, we are assuming that we are getting the efficiency based on the standards that we have.

DR. HSIEH: As you know, conjugation is a covalent binding, and it takes enzymes to split the conjugates. And that will affect the bioavailability, so that means you are--if your extraction scheme is not taking account of the conjugated form, then the analytical result is an

underestimate.

DR. OBERMEYER: Yes, again, it will be an underestimate. We only have certain standards that we can work from, so our best estimation is we are achieving, you know, a certain amount based on the standards that we have present. The conjugated forms I'm not really sure are present as a production standard.

DR. HSIEH: Dr. Fong, do you have any comments on the conjugated form of the ephedrine alkaloids?

DR. FONG: No, I can't comment on that. The data as I sit here running through my mind is when you are talking about extraction with methanol, and then people taking the capsule with the total extracts or with the herb in there, and what is the bioavailability? We really don't know what the patient is getting, at least in my mind.

Bill, do you have any insight?

DR. OBERMEYER: No. I believe the literature would probably support your thoughts.

DR. ASKEW: Dr. Fukagawa had a question. Has it been answered?

DR. FUKAGAWA: Yes, it has.

DR. ASKEW: Okay. Dr. Jasinski?

DR. JASINSKI: You were talking about the extracts, and I was asking a question of my colleague here,

and he wasn't sure of the answer. When people make the extracts for the commercial products, do they use a methanol extract? I mean, do they titrate it with acid and then they make a base and extract--do a chemical analysis? What is in the extracts, and what sort of salts of ephedrine--is it ephedrine base? Is it ephedrine salt in the extracts? And what are the salts?

DR. OBERMEYER: We're actually not sure of the Chinese method for making the 6 to 12 percent standardized extract. We have been looking for that, and we're not really sure what--

DR. JASINSKI: I'm looking at the products on the table over there, which has a bottle with an eyedropper which says extract.

DR. OBERMEYER: Right.

DR. JASINSKI: What's in that? Have you done an analysis of the ephedrine and the salts in there?

DR. OBERMEYER: We have done the analysis on many of the products, and we basically do them as the free base. So we're transforming--

DR. JASINSKI: So you titrate and take it down--

DR. OBERMEYER: HPLC, we're analyzing for the free base.

DR. JASINSKI: For the free base.

DR. OBERMEYER: Right.

DR. JASINSKI: So you have no idea what salts are in there or how that product is made?

DR. OBERMEYER: No. We're looking at analysis just of the free base. We're not doing titrations or anything else.

DR. DENTALI: I'd like to respond to that question.

DR. ASKEW: Directly to that question?

DR. DENTALI: Yes.

DR. ASKEW: All right. Go ahead.

DR. DENTALI: My understanding is that these products that are the industrial supply for what companies are buying and then placing in the capsule mixed with other ingredients are extracts of water and alcohol, not pH manipulated. So you may have high temperature water, alcohol, and that's why the concentrations typically are not higher than 6 percent, because if you extract everything in there, you're not going to be able to get an alkaloid concentration much higher than that.

DR. JASINSKI: So you just put it into a pot and add alcohol and water and you boil it up?

DR. DENTALI: Pretty much.

DR. JASINSKI: And then you take--

DR. DENTALI: Evaporate it off, put it on a carrier.

DR. ASKEW: We have questions by Dr. Benedict and Dr. Georgitis and Dr. Wang.

DR. BENEDICT: This pertains to the discussion of the assay procedure, and I'm sorry if you addressed this already. But as I understood it, you do a chloroform extraction and just run HPLC. Is there a reason why there's no protease K or some protease preceding the chloroform extraction?

DR. OBERMEYER: Okay. Actually, you misunderstood. The chloroform extraction was before on the tea when we had originally looked at the teas to look at if someone brewed a tea bag, what would be the extraction efficiency on it. The products do not have an enzyme added to them to help break them down. Most of the tablets are not protein matrix. They're just starch and things like that. So only two products that we have right now are actually the problem ones. We haven't gone to addition of--enzyme addition.

DR. BENEDICT: But if you're having a protein problem, I'm just surprised that you don't just get rid of it.

DR. OBERMEYER: It's possible. We've actually

just started really working on it, you know, recently.

DR. ASKEW: Dr. Georgitis?

DR. GEORGITIS: What is the percentage of binding to human serum albumin to the ephedrine with these various alkaloids? Have you looked at that?

DR. OBERMEYER: Personally, I wouldn't know that right off the top of my head. I wouldn't know the kinetics on that.

DR. ASKEW: Dr. Wang?

DR. WANG: I just want some clarification, when you were explaining to the sensitivity level you were able to detect. Let's say you have a 500 mg tablet, and it's the naturally ground-up stem. And, supposedly, how much can you recover on total ephedrine alkaloid?

DR. OBERMEYER: Generally what we do, we composite 20 tablets and then assay for a gram. We assay one gram of ground tablet, and our lowest level of sensitivity that we feel that we can quantitate accurately is 0.25 mg/gm.

DR. ASKEW: Dr. Ricaurte had a question, then Dr. Ziment.

DR. RICAURTE: I just want to make sure I don't lose the forest for the trees here. My understanding is that, on average, based on the kinds of analysis that the agency has done, you find that the total alkaloid content

per serving will vary somewhere between 7 to 22--up as high as 50, but on average about 20 mg of ephedrine alkaloid content. Furthermore, I understand that we don't know how much of that alkaloid content is active due to issues of bioavailability. Is that correct?

DR. OBERMEYER: Yes.

DR. RICAURTE: One question. Obviously you're dealing with the chemistry. Perhaps this is better directed to Ms. Hardy. Do we know anything about the pharmacology of these compounds from tests in animal studies other than the human study, uncontrolled studies that are available to us?

DR. OBERMEYER: I believe, to the best of my knowledge on the literature, the interactions between all the alkaloids have not been fully scientifically--

DR. RICAURTE: What I'm specifically referring to, for example, it would be of interest to me to know on a dose equivalency if you were to compare one of the "typical" products, compare it to a standardized stimulant, use L-ephedrine(?), use amphetamine, use standardized animal protocols. What I'd like to know is how much of that product is equivalent to, say, 5 mg of ephedrine or 5 mg/kg of amphetamine? Obviously that would require some animal--is that data at all available?

DR. LOVE: There is very sparse animal data, and

one of the problems with animal data is there is known species differences in the metabolism of all of these alkaloids. So, therefore, mouse and other rodent data isn't directly relevant to human experience. It's very hard to extrapolate from mortality and morbidity metabolism data that is done in rodents directly to that in humans. In humans in particular--and I'll bring it up--we know that a significant portion of the ephedrine is metabolized in the body to norephedrine, so you have additional effects that are due to secondary metabolism. This doesn't occur in a number of the animal species, so it's very hard to predict what these effects are going to be from these combined combinations of alkaloids, and then compare it with what is known with pharmaceutical single preparations of, say, ephedrine, pseudoephedrine, or phenylpropanolamine. So it is very problematic.

DR. RICAURTE: In all fairness to the manufacturers, then, it becomes very--there is the temptation, at least on my part, to use what we know about ephedrine and related alkaloids and generalize to what we're discussing. Yet in part what I'm hearing is because of species differences, dose differences, et cetera, that could be fraught with problems. I guess I can't help but think of Dr. Kessler's comment. You know, that is a problem with all

agents that you folks regulate not only as foods but as drugs, but we have to have some starting point. If on the one hand we're told we can't generalized, it really leaves me at a bit of a loss.

DR. LOVE: It's not that you can't generalized it. You have to put all the data in the context of what is known and then try to grapple with what is reasonable when you're looking at your safety perspective from a scientific view.

DR. ASKEW: Dr. Ziment?

DR. ZIMENT: This is really, I think, a question for Ms. Hardy. I know that ephedrine and ma huang are not usually smoked, cigarette-type preparations, but there is a nasal preparation, and I wonder if that's being used or studied or considered as a substance of abuse or a route of abuse.

DR. YETLEY: Maybe I could just answer, and then if Connie has something to add, she could. But the nasal use would not be legally marketed as a dietary supplement; that is a drug.

DR. ASKEW: Yes, Dr. Applebaum?

DR. APPLEBAUM: I just have a question concerning the data that was provided on the active ingredients that are found in the dietary supplements, and, Dr. Yetley, you made mention of the fact that you're looking to the Advisory

Committee in terms of identifying adverse synergies amongst these, or--I wanted to refer back to--

DR. YETLEY: The question is a very open-ended one, but if the Advisory Committee feels that there are safe conditions of use that they could--or safe levels that could be used, then we would like some discussion, some input on the concept or on the idea or on the question, I guess I should say, as to whether or not this multitude of other ingredients which could well have some kind of interactive effect is an issue that we should be concerned about, in what way should we be concerned about it, how should we deal with it. It's an open-ended question in which we're trying to use your expertise that you bring to the table and get some feel for that, because you are dealing with very multi-ingredient products, which is quite different than what we usually think about.

So the first question is: Is that part of the safety concern? Is that contributing or is it likely to contribute in some way to the risks that we're seeing? And if so, what kinds of solutions do we have available to us to deal with it?

DR. APPLEBAUM: And then a point of clarification. There are no guidelines regarding the formulation of these products; correct?

DR. YETLEY: No, it's the manufacturer's call on the formulation, and the ingredient list lists the ingredients by order of predominance. The label information does not require that they have quantitative amounts.

DR. APPLEBAUM: So I'm not going to make the assumption that there's a reason for the combinations that are found?

DR. YETLEY: You'd have to ask the manufacturers.

DR. ASKEW: One final question by Dr. Croom, and then we're going to go into our break.

DR. CROOM: Maybe this will be under the safety, but I'm wondering, since I did submit some questions along these lines to the exec. sec. two weeks ago to say do we have correlations with product brand manufacture with adverse events, commercial source of the plant material, type of GNP, extraction process of the extracts, water versus aqueous alcohol, levels of ephedrine alkaloids, variation in individual serving or dose units, any other plant and the product--your question--but not limited to caffeine-containing plants. What my question is: These are all product quality and formulation issues. Do we have a way to take the actual adverse events, not general means but adverse events, and relate these to a product quality issue to help us settle this?

DR. LOVE: Well, since we have none of that information available from the manufacturers and they're not required to supply it, maybe you could answer the question.

DR. CROOM: No, this question was asked of could we correlate that to the adverse event situation.

DR. LOVE: You have the information in some of the briefing materials that were given you. On each case that we received, there is an indication of the product if that information was available to us, and you can look also at the description of the adverse event. Did we do an evaluation of that? No. It's really beyond what we have data to do.

DR. CROOM: Thank you.

DR. ASKEW: Dr. Love has a rather lengthy safety evaluation to present, and I think we'll take a break before we go into that, Dr. Love. We'll return at 3 o'clock, and then we'll have open public hearing after that.

[Recess.]

DR. ASKEW: If you would resume your places around the table and those of you in the audience regain your seats, we'll go ahead and get started here.

Before Dr. Love gives her presentation, Dr. Yetley would like to make a statement of clarification. That certainly would be appreciated, Dr. Yetley. We look forward

to this.

DR. YETLEY: I'm not going to clarify everything.

DR. ASKEW: Every little bit helps.

DR. YETLEY: It's a simple one. I just wanted to clarify that, after all this discussion of methodological problems and what-not, the data that we're using in the market survey as well as the data that Dr. Love will use when she looks at patient--or at consumer intakes are based on data in which we had confidence. We do have some methodological problems. We have not used those data. We have used data that we had confidence in. So, yes, there are methodological problems in terms of looking at the entire marketplace, but we have tried to limit our use of data to that which we have confidence in. I just wanted to clarify that.

DR. ASKEW: Well, thank you. I think that increases the confidence level a bit.

We're ready now to go into our safety evaluation report, and Dr. Lori Love from the FDA will give us the presentation on the safety evaluation of the ephedrine-containing alkaloid compounds.

DR. LOVE: Thank you. Today I will briefly summarize the various forms of data that provide information about the safety of ephedrine alkaloid-containing products.

More extensive information on this subject has been provided to the committee in the briefing book and addendum.

May I have the first slide, please?

Information about the safe use of a particular product can be obtained through a variety of mechanisms, including basic and clinical studies, as has been discussed here today, that may be conducted during the premarket period of development. But these studies are usually limited in a number of ways, including there are small numbers, age differences, subject durations, et cetera. Because of this, much of the kind of information that becomes available on any type of product marketed, whether it's a dietary supplement, drug, or device, and how FDA learns about it and its potential safety problems, occur in the postmarketing period. So how does FDA learn about these problems, as shown in this slide.

It's very complex in the Center for Food, and as indicated here, these come in a variety of forms and through a variety of mechanisms from the consumer, to congressional, to our Office of Regulatory Affairs, correspondence, could come through health care professionals, state health departments, feeding in through MedWatch, we get reports from some manufacturers, and they all feed into our system of adverse events.

We routinely enter all of these adverse events into our surveillance system, which we call SN/AEMS, which is Special Nutritional/Adverse Event Monitoring System, and follow-up is routinely attempted on all serious adverse events or those deemed clinically significant.

So much of what we learn about potential adverse events is discovered after marketing, and we think that postmarketing surveillance is probably the most useful indicator of potential safety problems associated with the product. There are, however, a number of recognized limitations to the interpretation of the data, but its strength is that it provides information that's not available in the premarket period. It identified adverse effects that develop with chronic use or exhibit latency; it shows adverse effects seen in special groups; and it shows adverse effects that occur with relative infrequency. These are things that you won't discover during the premarket period of review.

The issue we are grappling with today and tomorrow is how to use the available information to evaluate what could be a safe level of use and conditions for use for ephedrine alkaloid-containing dietary supplements. We're trying to do this by integrating all the different types of sources of information, including those from adverse events,

the scientific literature, et cetera. When we have a well-documented adverse event report where there are known conditions of use, sufficient information to evaluate the adverse event such as the type and severity, its association with the product use such as the temporal relationship, whether there is dechallenge and rechallenge information, and adequate information about the product including its ingredients, their potencies, interactive effects, et cetera, we can really evaluate such information. Unfortunately, we rarely have all these pieces of the puzzle to allow the interpretation of an adverse event report on an individual basis, and this is where summary information from a signaling system such as a postmarketing surveillance system becomes important, because it can provide information about the types of products that are associated with particular adverse events or particular patterns of adverse events. It gives us information on the demographics of the population, et cetera, and that's what I'm going to try to provide today.

This next slide shows the cumulative number of adverse event reports that have been entered as of yesterday--I updated this slide in the packet for you--and we have more than 800 adverse events that are reported on ephedra-containing products; 371 of these have been reported

just in 1996, and this is more than we presented to the committee last fall as a total number.

Clearly, some of this represents reporting biases over time, and we have publicized our safety concerns on ephedra-containing products a number of times. In 1993, here in June, we initiated the MedWatch program. In 1996, we initiated the ephedra consumer hotline. However, overall, we believe that adverse event reports on dietary supplements similar to other products that we regulate are vastly under-recognized and under-reported.

This is to go specifically about the population that I am going to talk. I said there's 800 today. Of course, we haven't been able to evaluate these. We've evaluated approximately 603 products where ephedra alkaloids are either known to occur or suspected of occurring in the products. And, again, these account for the majority of adverse event reports that we received on dietary supplements total.

Similar to what was done in the market review, we have attempted to classify these products into broad categories, and for my categorization, I have made them weight loss/energy, because many of the products have both types of claims, the ergogenic/body building products, which are seen here in yellow, and what is labeled here is

youth/abuse, but it is better known to you as street drug alternatives, being the purple here. Clearly, the weight loss/energy represent the majority of adverse events that we see, 92 percent, and it's not these other types of products, although there is some overlap between ergogenics with weight loss-type products.

In looking at demographic factors, we see with age here it is 0 to 19, 20 to 29 here, 30 to 39, 40 to 49, and then 60-plus, the majority of adverse events occur in young to middle-aged adults. We're talking about the 20- to 49-year-old population, and the majority are women, 74 percent. So 72 percent of the adverse events occur in the 20- to 49-year-old population, and 74 percent of those are women. Now, this may represent a little bit of the type of products that they're using, which are weight loss and energy type products.

The majority of these adverse events occur within one month of use. Fourteen percent occur on the first use or with the first day of use, as shown in red. If you look at these, the first day and first week of use, within the first week of use this accounts for 35 percent of the adverse events that we see. So a third of the adverse events occur with only a week's use. Fifty-eight percent occur within the one month, and then you see the stragglers

with more long-term use. So we see both acute events that occur with first use, and we see chronic events that occur with long-term, more than one month's worth of use.

In looking at the type of adverse events that occur, we've tried to classify them into the various organ systems, and the majority of serious adverse events fall into two major organ systems; that is, the cardiovascular system and the nervous system. And the cardiovascular system is probably the major cause of both mortality and morbidity in this population. Overall, the death rate is 4.3 percent. This is counting all deaths within our total number of 603 population, and then looking at cardiovascular versus other causes.

When we look at the yellow here, this is all serious cardiovascular adverse events. This is the cumulative of this number. This is approximately 14 percent. Myocardial infarcts and ischemic events occur in 6 percent, dysrhythmias in 5 percent, strokes in 4 percent, and cardiomyopathies occur in just under 1 percent, and that's actually an interesting population. It's a small number, it's all males, and it's all long-term use of the product.

So what we see are heart attacks and strokes in asymptomatic individuals with normal coronary or cerebral

arteries. They are, again, more common in young women. These women would not be expected to have significant risk factors for cardiovascular disease, and they primarily involve ischemia. They're not atherogenic in nature.

This is the slide that summarizes our experience in nervous system adverse events. Again, approximately 16 percent total serious nervous system adverse events overall, and these break down into 4 percent seizures, 7 percent psychiatric, which includes acute psychosis, mania, acute depression. Vestibular is an interesting category. We have vestibular dysfunction as manifested by vertigo and inner ear signs. Again, it appears to be more associated with chronic long-term use of the product, and LOC is loss of consciousness, and this is sometimes associated with traumatic accidents, including motor vehicle accidents. Again, this accounts for significant morbidity in our population.

Of the adverse event reports received by FDA, the majority of persons sought some kind of health care, whether from their local health care provider, the emergency room, or actually even being hospitalized, and many people received extensive evaluations and workup to try to document what the cause of the adverse event was--overall, about 78 percent. In looking at factors associated with it, not only

is there a temporal relationship associated with the use of the product in the majority of these cases, but there's also evidence of positive dechallenge in 27 percent and rechallenge in 4 percent of the patients--again, implicating the product as being the cause of the adverse event.

The next two slides are summary slides that just show the different patterns of signs and symptoms that have been reported with dietary supplement products containing ephedrine alkaloids. The two major classes, as I stated, are cardiovascular and nervous system effects.

What we consider significant or serious cardiovascular include dysrhythmia, severe hypertension, cardiac arrest, angina, myocardial infarction and stroke. Less clinical significant include tachycardia, mild hypertension, palpitations.

For the nervous system, serious adverse events include psychosis, suicidal, altered or loss of consciousness, which would include disorientation or confusion, and seizures. Those we deem to be less clinically significant include what has been typically called stimulant type of effects, including anxiety, nervousness, tremor, hyperactivity, insomnia, altered behavior, memory changes.

Other organ systems can be involved, including the

gastrointestinal system, where we have seen serious adverse events including altered levels of serum enzymes and hepatitis itself. Again, less clinically significant would be GI distress--nausea, vomiting, diarrhea, et cetera.

There can be some quite significant dermatologic reactions, including exfoliative dermatitis. These are consistent with an immunological basis and are well known in the scientific literature for ephedra-containing product. Then there can be the general manifestations, which include numbness, tingling, dizziness, fatigue, lethargy, and weakness, as well as other organ system involvement, including myopathy.

What I have tried to do here now is to provide a few examples of adverse events in which there are no or few apparent complicating factors, because as was kind of indicated this morning, there are complex histories on many of these, and you have to take it. The data are what the data are, and you have to evaluate it and put it into context. For illustrative purposes, I just wanted to discuss a few of these.

The first is a 35-year-old female who was on no medication, had a negative past medical history, who developed a non-Q wave myocardial infarct while using the product within the dosage range recommended on the label.

She had used the product for approximately 30 days, had stopped it for one week while on vacation, and then had re-initiated the use of the product. About 11 days after re-starting, she developed acute throbbing, anterior chest pain at rest, radiation to her left shoulder, numbness of left arm and hand, diaphoresis, and shortness of breath. In the hospital, she had electrocardiogram and cardiac enzyme changes indicative of a myocardial infarct, felt to be secondary to coronary artery spasm. Cardiac catheterization showed normal coronary arteries.

In this case, we have a 28-year-old male who had used a product for approximately one day, one capsule every day or one capsule twice a bad, which was half the recommended dose, for energy. His father found him on a rental property, having taken the car out there, responding inappropriately and being bloody. He was taken to the emergency room where his blood pressure was 168/90, a pulse of 116. He ended up having a computerized tomography and an MRI of the head, EKG, encephalogram, echocardiograms that were all normal. His diagnosis was syncope and a closed head injury. The neurologist that evaluated him felt "most likely he had a seizure secondary to ephedrine" from the health food substance he was taking.

In this case, a 35-year-old man used the product,

two capsules at noon and three capsules at 4:30 p.m., and he did a vigorous workout for the next hour starting at 5:30, which was pretty usual for him because he considered himself an amateur trained weightlifter. And as I noted, the recommended dose was two capsules before each meal not to exceed six. He started experiencing chest pain at approximately 7:30 p.m., was hospitalized with an acute myocardial infarct with consistent electrocardiogram and enzyme changes. Subsequent cardiac catheterization again reveals normal coronary arteries.

In this case--Dr. Kessler has alluded to it before--we had a 20-year-old male college student who took eight tablets of an ephedra-containing "street drug alternative" as recommended by the salesperson, although the label instructions were to take four and not to exceed four in a 24-hour period. He took this at approximately 4:30; within about 30 minutes, he started complaining of being hot, sweating, and having a severe headache. He decided not to go out with his friends that night and was found dead by his friends approximately 8 hours later. The coroner's report stated that the cause of death was "cardiac arrhythmia due to the synergistic effects of ephedrine, pseudoephedrine, and phenylpropanolamine, and caffeine."

The final case--again, alluded to by Dr. Kessler--

was in a 24-year-old male college student who used an ephedra-containing ergogenic product for approximately two years, within the directions as indicated on the label, along with several other dietary supplements that were mostly vitamin and mineral preparations. He was stated to be previously healthy, with a healthy life-style. He was found dead by his sister. The coroner's report reads the cause of death is "patchy myocardial necrosis associated with ephedrine toxicity from protein drink containing ma huang extract." The label information on this product indicates that there was approximately 20 mg of ephedra alkaloids per serving.

In the next few slides, what I would like to do is summarize the results of the FDA analysis on products associated with adverse event reports where we had information on how the consumer used the product so that we could calculate the milligrams per consumer use. And what you see here is we have a number of 35 on this, and if you look, you have a spread in all of these products that range from one product at 0 all the way up to over 50. The mean on these products is approximately 30 mg plus or minus 31. The median is 25. So at 25 mg, 50 percent of the products fall above this value, and 50 percent fall below that level.

If you look at it on the basis of milligrams per

serving now, as recommended on the label, the median is approximately 21, which is very similar to what Ms. Hardy told you in the market survey. Actually, we have looked at all products that we have that are consumer-related whether they're ones that we had specific information on how the consumer used it or it was another sample collected at the time that the adverse event report was taken. Again, the median on these products is approximately 20 mg per serving for total ephedrine alkaloids.

In this one, we're looking at ephedrine versus total ephedrine alkaloids, and the mean here is 10.4 There actually is an error in this one slide. It's the next slide, excuse me. I'll show you. They, again, range from one product at 0 all the way up to 50. The median is 7.8 mg, as the consumer used it. If you use the milligram per serving, it's 6. So very low levels, and, again, if you look at all the samples we have, the median level is 4.8. So it falls right in here, 50 percent above, 50 percent below.

To show that there can be marked product variability in the content of ephedrine alkaloids, I took two examples that will be labeled Product 1 and Product 2 just to show where we have repeated samples of the same product. And, remember, the manufacturer can change

formulation at any time, but there is natural product variability. So in Product 1 here, we have a range from--this is actually a 0 here--0 to 25 mg of total ephedrine alkaloids, and for ephedrine we have a value from less than 1, again 0, up to 10 mg.

In Product 2, where we don't have quite as many samples, but, again, we can see that there is a broad range in the total ephedrine alkaloids that can be found in these products, as well as a range in the total ephedrine as an isolated value. That is something that we need to consider, that there is a pattern of alkaloids that appear in these products. They can differ depending on what source the manufacturer is using for a particular batch, and there can also be, as Dr. Obermeyer indicated, matrix effects and other effects that affect the bioavailability of these products.

So to summarize, the cardiovascular system effects are predominantly ischemic. They're not atherogenic in nature. We see strokes and myocardial infarcts in asymptomatic individuals with normal coronary or cerebral vessels, although we admit that most cases are complex with patient factors that make interpretation and attribution of individual adverse events problematic. However, it is important to emphasize that these adverse events have been

reported across a broad spectrum of the population and include examples in which there are no or few complicating factors. When we look at central nervous system effects, the major serious ones are psychosis, manias, seizures, and, again, these adverse events appear to result from sympathetic nervous system stimulant effects and are consistent with known physiological and pharmacologic effects of ephedrine alkaloids.

Looking at our data to date for the purposes of the classification criteria, as I stated, there are 600, but we now have more than 800 to date adverse events involving more than a hundred products, and remember that these products are not standardized. They have different ingredients, type of ingredients, source of ephedrine alkaloids, different patterns of alkaloids. So you can't readily compare them. But the one common link is that they all have an identified source of ephedrine alkaloids in them, and further, there is a temporal relationship between occurrence of the adverse event and product use. It often occurs early after the product is first started. It may occur with the first use or with the first week of use. And signs and symptoms often remit when the product is discontinued.

In a few individuals, there is positive

dechallenge and rechallenge information, again, making attribution to a particular product stronger. Adverse events are reported as occurring in the healthy young population, as well as those with underlying diseases or conditions, and I believe this is where our data differ from the Texas and Ohio experience. And the adverse events are reported when the product was apparently used according to label instructions, which appears to be in the majority of the individuals where we have evaluable data.

So I think our conclusion just from our information that we have on adverse event monitoring is that there is a consistent pattern of signs and symptoms across many cases with different patient factors that all appear to be the result of sympathetic stimulation involving predominantly the cardiovascular and central nervous systems, and that, further, these types of effects are consistent with the known physiologic and pharmacologic effects of sympathomimetic agents such as the ephedrine alkaloids.

What I briefly would like to do now, since people have asked questions--and I'm just going to highlight the area; we've provided more information in the briefing book--is to talk a little bit about the pharmacology of ephedrine alkaloids. And I think the known pharmacology is a good

starting point for looking for a basis to evaluate and interpret various adverse event reports, particularly those with foods.

Ephedrine and related alkaloids elicit physiological responses similar to those found in catecholamines, a class of neurotransmitters in the body that act on the sympathetic nervous system, and that's why they're called sympathomimetic agents.

This is an extremely diverse class with multiple effects, and I'm not going to go through all of these, but what I'm going to show here is the adrenergic receptor activity and indicate that they're different depending upon the particular alkaloid you're talking about. So for ephedrine you have a lot of beta receptor effects which are predominant in the cardiovascular system and account for many of the type of physiologic and adverse events that you see because of the effects on the cardiovascular system. Pseudoephedrine is much less potent in this area. Phenylpropanolamine has more alpha adrenergic effects, as does norephedrine. And the one not listed here because we generally don't have a lot of information in the English literature would be methyl ephedrine, another alkaloid that can be seen in levels that could be significant in these types of products.

Remember, we see a mixture of all these alkaloids in dietary supplements using botanical sources. So you could well expect interactive effects from these different receptor patterns. If your predominant alkaloid was ephedrine, you would expect very strong beta effects as well as a strong central nervous system effect. But if you had more norephedrine with the ephedrine, you could be picking up more alpha.

Since they used different sources, this is something that is very difficult to evaluate. It's probably going to be very difficult to standardized. But we certainly have to consider it in our safety equation.

What I have tried to do here--and I don't know if people can see it--is talk a little bit about the pharmacokinetics of ephedrine alkaloids. Ephedrine itself, all of the products, ephedrine, pseudoephedrine, and phenylpropanolamine, are well absorbed from the GI tract. There's essentially 100 percent absorption. Only ephedrine has significant tissue accumulation in the liver, kidney, spleen, and brain. The half-lives are all approximately four to six hours. They're metabolized in the liver and really only ephedrine is significantly metabolized in anywhere from 20 to 45 percent is metabolized in the liver. Its major metabolite is norephedrine. And so you can get

secondary effects from norephedrine in the receptor pattern because of metabolism in the body. All are excreted in the urine. If you make the urine more alkaline, you decrease the urinary excretion, and you will increase the blood levels.

In looking at individual cases in the scientific literature or actually looking at some of the individual studies, there's no clear correlation between any administered dose and a subsequent plasma level of ephedrine and related alkaloids, nor with any particular pharmacologic effect. And I think that's because patient factors are very important in how you metabolize ephedrine, how sensitive you are to it, its effects, et cetera. But there's not good scientific data that would allow you to do a dose response for particular effects, but particularly for particular adverse effects.

What I've tried to do here is summarize factors that influence the sensitivity to any sympathomimetic agent, including those of ephedrine alkaloids. These include age, so children and the elderly are known to be more sensitive to sympathomimetic agents; genetics, how you metabolize the alkaloids--if you're a slow metabolizer, you're going to have higher blood levels longer, and you may have more adverse effects at a particular dose; certain physiologic

states, including pregnancy or lactating; hyperdynamic states, including exercise where you may increase your receptor sensitivity in the heart or in organs; weight, obesity, obese patients, truly obese patients are known to be less sensitive to sympathomimetic agents. The closer you are to normal weight, the more sensitive you are. There is also some information that women may be more sensitive to certain sympathomimetic agents.

Dieting practices could affect it. So if you are undergoing severe caloric/fluid restriction this should be-- that may well affect it, as are other types of dieting practices. Medications and foods, these have been alluded to before. The monoamine oxidase inhibitors, methyldopa, beta receptor blocking agents, caffeine, and other stimulants could well have interactive effects with this. Concurrent diseases or conditions, particularly cardiovascular, thyroid, or prostate, also renal because conditions that affect renal blood flow will affect the metabolism and blood levels of ephedrine alkaloids, and what has been loosely called autonomic dysfunction. And duration of use appears to be important.

People talk about tachyphylaxis developing with short-term use, and tachyphylaxis is a phenomenon where you take the product, you get the stimulant type of effects, you

keep taking it and these go away. Well, if you stop it for a dose or a day or a couple days and then start it again, which is the practice when you're taking these long term, you lose tachyphylaxis. So you have both acute short-term effects as well as the chronic long-term effects that are alluded to with the cardiomyopathies that need to be considered and may be due to different patterns or uses of the product or risk factors of populations that are difficult to do.

Now, this morning some of the clinical trials employing the pharmaceutical preparations of ephedrine plus or minus caffeine plus aspiring were alluded to, and I just wanted to briefly talk about them. These were talked about last fall. They're included in your briefing book. The purpose of these studies was to evaluate again pharmaceutical preparations of ephedrine, either singly or combined with caffeine, plus or minus aspiring, on weight loss in the treatment of obesity. These were very carefully controlled, double-blind, placebo-controlled trials where patient risk factors such as hypertension, et cetera, were evaluated and those patients were not enrolled in the study. So they tried to take care of what would be confounders to the interpretation of study results, underlying diseases, conditions, risk factors, drug usage. The primary outcome

was the effect on therapy on weight loss, not the safety of the product.

Again, you have to recognize that clinical trials have marked limitations, just as postmarketing surveillance type studies in clinical trials. There's often too few subjects. It's a narrow, targeted population so you can't generalize the information from an obese population to the general population. It was a very short duration where they looked at this for the evaluation period. In many of these studies, although they've been published in the peer-reviewed literature, there's selective presentation of the data in the published reports, multiple publication of the same data, et cetera. But most importantly, the studies were not designed to evaluate the safety of these pharmaceutical preparations.

However, they're very important because they indicate that adverse effects occur, and they occur more in the ephedra with caffeine, which was greater than the ephedrine, which was greater than the caffeine, which was greater than the placebo, such that 44 percent of those taking ephedrine only had adverse events and more than 60 percent with the ephedra/caffeine. The pattern and types of adverse effects seen in these trials are consistent with the known effects of sympathomimetic agent. Again, it was

increased heart rate, blood pressure, and stimulant type of effects. And they were most common in the early treatment period, although in some cases they did extend throughout the treatment period.

Cynthia Culmo from Texas this morning just alluded to historical use versus what is current use in dietary supplements in the market today, and I just wanted to touch base again with that and just go down the differences in product, category, and how it's used, et cetera.

Historical use in traditional Chinese medicine was as a medicine. It was a health care practitioner; an herbalist prescribed after seeing a particular patient and evaluating him. It was often used for respiratory disorders. The particular formulation was health care practitioner selected again, and they were using defined herbal combinations prepared in defined ways. The duration of use was typically short term.

In dietary supplements today, it's a consumer-selected product. It's most often for weight loss/energy, but there's many other uses. These were not considered in traditional use at all. The formulation is manufacturer-selected. It's a combination of ingredients that have not been used traditionally, and the duration of use is undefined and can be prolonged.

In neither of these systems, but particularly in traditional Chinese medicine, there was no mechanism for collecting adverse events, although I believe that it's well recognized that they could occur. There were many cautions that you couldn't use particular herbs in particular patients after evaluating, or you couldn't use particular herbal combinations together with others. And, again, when you're talking about the formulation, you're talking about the whole herb prepared in a tea form. In the dietary supplement it's extracts and other forms than those used traditionally.

So a general summary, just looking at evaluation of association between adverse events and the use of ephedrine alkaloid-containing dietary supplements, there are a number of variables that are looked at when you're looking at attribution. These include the strength of the association, and I believe the data from controlled clinical trials indicate that a significant portion of healthy individuals can experience adverse effects. There is a consistency of the association, and I believe that data from all our sources of information, including the scientific literature and those seen with our adverse event reports, indicate that these effects are possible in otherwise healthy individuals. The clinical pattern of signs and

symptoms appears to be consistent across all sources of data and predominantly cardiovascular and central nervous system effects, which is consistent with what is known about the known physiology and pharmacology of ephedrine alkaloids.

There is a temporal relationship between exposure and onset or improvement of disease and conditions in many of these cases. There is a possibility for dose-response relationship, particularly at toxic levels, although this is much harder to grapple with, particularly since there's no product standardization and there's multiple ingredients that may be interactive and may be contributing to the effects. And there's a plausible pathogenesis here in that it's sympathetic nervous system stimulant effects, it's supported by experimental evidence from controlled clinical trials, which reveals a similar pattern of adverse effects.

So I think our bottom line conclusion here is that there is a consistent body of evidence from adverse event monitoring, case reports from the scientific literature, which I did not discuss today but which is in your briefing book, and controlled clinical trials that indicated association between the use of products containing ephedrine alkaloids in subsequent adverse events is possible. And I do note that adverse events for these botanical preparations are noted in the scientific literature and have been noted

for a long time, including back to the 1930s, and even in the very early literature they recommend test dose of ephedrine alkaloids in the range of 10 mg because they recognize individual sensitivity almost as a normal pattern and not the exception.

I think I'd like to close here and take questions.

DR. ASKEW: Thank you, Dr. Love. I think that presentation has been quite helpful, and perhaps we should have had it a little earlier in the proceedings. But I think that it's been helpful.

I'd like to open it up now for questions from the committee. Dr. Ziment?

DR. ZIMENT: I'm looking at your chart on the adrenergic activity of sympathomimetic agents, and this may or may not be correct where you classified the alpha beta 1 and beta 2 effects.

DR. LOVE: That was taken from a classical pharmacology textbook.

DR. ZIMENT: I don't doubt it, but the information may be crude and--

DR. LOVE: Granted.

DR. ZIMENT: And even the classification may be too crude. But the important point here that I wanted to make is that beta 2 activity can be excluded as being

harmful because we do us a lot of pure beta 2 drugs, which certainly don't cause these side effects that we're worried about.

Beta 1 side effects, which are reasonably potent with ephedrine, are not seen with phenylpropanolamine. On the other hand, phenylpropanolamine has more alpha adrenergic effect, and in actual fact, alpha adrenergic effect on blood vessels are the opposite of beta 1 adrenergic effect. So the real question is: Is it the alpha or beta 1 effect which is most important here?

DR. LOVE: Or is it a beta 3 or something we haven't identified.

DR. ZIMENT: Or something else. But it sounds as though high blood pressure and vasoconstrictive episodes, being cardiac ischemia and strokes, are more likely to be alpha effects. This would suggest that ephedrine, which also has beta 1 effects, is less potent than phenylpropanolamine in causing these adverse ischemic effects. But that doesn't seem to be borne out by the facts that we've had on phenylpropanolamine.

Of course, some people would argue that ephedrine in the form--or at least ma huang, with all its components, might balance the alpha 1 and the beta 1--the alpha and beta 1 effect and, therefore, may be somewhat safer than a pure

alpha adrenergic agent. There's a difficulty here and maybe the difficulty is simply that this chart is wrong.

DR. LOVE: Well, it's a simplistic chart, and we know much more today and we'll know much more tomorrow about receptor types and how they're metabolized in individual sensitivity. But as I indicated, there are host factors that affect sensitivity even to individual receptors, including exercise, gender, et cetera. So it is a very complex story.

DR. ZIMENT: Yes, but it's not individual. Ephedrine-sensitive and phenylpropanolamine-sensitive receptors are the same receptors.

DR. LOVE: It's the same receptor, but you're comparing a defined product as a single ingredient with a product that has a whole spectrum of alkaloids, and a spectrum of alkaloids including those that could be metabolized in the body.

DR. ZIMENT: Right. And furthermore, you point out in the chart below this some pharmacokinetics that ephedrine's major metabolite is phenylpropanolamine.

DR. LOVE: Is norephedrine, actually.

DR. ZIMENT: So, again, there's something odd here. Why isn't phenylpropanolamine a more dangerous drug that ephedrine?

DR. LOVE: It's probably related to its potency, but--

DR. ASKEW: We have a number of people here that wish to comment, and I would like to follow up. If there's a comment that's directly related to what Dr. Ziment was talking about, we'll go to that next, and then we'll go to our other people. I think Dr. Woosley would like to comment directly on this.

DR. WOOSLEY: Yes. First I'd like to tell Dr. Love I think this is a very compelling and well-presented analysis of a very large data set that's quite disturbing. In response to the question about receptors and drug action, I think the table that you chose, as you said, was one that is from a classical textbook which describes the effects of these drugs in organ systems and in pure forms. And what we've learned in the last few years and I think what Dr. Love alluded to was that we are not equivalent in that way. We don't all have the same alpha receptor or beta receptor or beta 1. We are a distribution, and within that distribution, we already know that there are polymorphisms and mutations of these receptors that give very different and sometimes aberrant responses to a drug that is well tolerated in an organ bath and maybe not giving you--does not give you the predicted response and is probably

responsible for the vasospasm, the extreme sensitivity of the coronary arteries, which is a common feature with all of the sympathomimetic amines.

I think there is nothing surprising in this database. This is exactly what one would expect from administering a sympathomimetic amine in an uncontrolled, unscreened fashion to thousands of patients, and this is exactly what we should expect. This is the kind of thing that happens when you have variability in formulation, variability in metabolism, variability in receptor density, potential interactions with the diet. We don't have a lot of data on ephedrine, although it's quite an old drug. But what we do know indicates that it probably will interact with foods in the diet such as other drugs metabolized that are similar and probably in the 3-A family. And things like grapefruit juice, which block the metabolism of many drugs, could be--something like it or maybe even grapefruit juice could be causing an interaction such that even a very safe amount of ephedrine in a large population could be lethal in a significant number of people. And I think the bottom line is there are many deaths, many more deaths, I am reminded, with this compound than prescription drugs that are still on the market and are not going over the counter.

I am reminded of the experience with the non-

sedating antihistamines which have this kind of death profile. Cardioselectivity, seems to be predominant in women, we know now that women have totally different expression of K channels in their heart, and it may be potentially related to this action.

So I think this is a very consistent and compelling database.

DR. ASKEW: I think, Dr. Woosley, that your comments help clarify the lack of correspondence between dose and adverse incidence based upon what you said, and it certainly helps clear up that particular--help us clear up that thing.

We've got several people who want to speak, and I'd like to list the order in which we'll go to them so you will know when you are going to get your chance. Dr. Benedict, Dr. Chassy, Dr. Fukagawa, Dr. Jasinski, and Dr. Katz have indicated that they want to comment. We'll go first to Dr. Benedict.

DR. BENEDICT: I'd like to first of all echo everyone's enthusiasm for your presentation, and I'd like to just clear up a couple of things that I probably just missed as you said them.

In the one case of chronic dose where you talked about 20 mg per dose over a number of years led to really

seriously adverse events, do you have any idea of how many doses per day that was?

DR. LOVE: All indications that we have is that the consumer used it within the directions of use as indicated on the label, and I don't have it front of me, but you could, of course, look it up in the record. That, unfortunately, is one of these products where we're still analyzing it ourselves because of its protein matrix. And the label value indicated that there were approximately 20 mg of ephedrine alkaloids.

DR. BENEDICT: And in terms of an acute dose that leads to a seriously adverse event, do you have a feel for the strength of that acute dose in just a few cases?

DR. LOVE: I can tell you that looking at what I presented as the median dose of the total ephedrine alkaloids, those were in consumer samples where we had adverse events, many of them serious, where the median is approximately 20 mg of ephedrine alkaloid, meaning 50 percent fall above that and 50 percent fall below that. I know for total ephedrine that we have serious adverse events in the 1 to 5 mg range.

DR. BENEDICT: I was afraid you were going to say that. And the last thing is: Can you elaborate a little bit about the difference in your results in young versus old

from the Texas and Ohio experiences?

DR. LOVE: Well, we've looked at--actually, some of the data that we have are from Texas and Ohio. What we have done is tried to get follow-up and verification in all cases where we could and actually evaluate them.

Texas and Ohio's data includes OTC drug products. This database does not. Where we identify a product afterwards as an OTC drug, we get a label, we find out that it's a drug, it's taken out of our database or corrected if it doesn't have a source of ephedrine alkaloids in the label or labeling or other information given to the consumer. Sometimes it's not on the label itself, but on other provided information that the consumer receives. So we're constantly updating the database and trying to correct it, but drug products are not included in our database.

DR. BENEDICT: Thank you.

DR. ASKEW: We'll go now to Dr. Chassy.

DR. CHASSY: First let me check a number. Is the median of ephedrine alkaloids in these consumer samples that you looked at--this is really going back to the previous talk--about 20 mg?

DR. LOVE: As the consumer used it, it's slightly higher than that. If you look on a milligram per serving basis as instructed in the labeling instructions, it's

approximately 20 mg. So it's in the 20 to 25 mg range for where we have information on consumer use.

Now, if you look at all products that we had--and there were multiple samplings--it's approximately 20 mg.

DR. CHASSY: Okay. I'll tell you where I'm going. One of the charges of the committee is to try to come up with a recommendation about what a safe or reasonable level of intake would be, and I think there are some numbers that you may not have but we'd love to have. One of them is some idea of the number of people in this country that are taking these products, some idea of the number of cases or incidences of adverse effects per 100,000 population, you know, like we would normally look at, and some ability to normalize this data. You've got a dose-response curve that plots the number of incidences of adverse effects--

DR. LOVE: Actually, it's number of reports. You can't do incidence or prevalence data from adverse event reporting.

DR. CHASSY: Right, you've got a number of reports, and because you had a case history, you make in many cases, at least what the label says the potency of the stuff is, I suppose, because you couldn't analyze the sample they actually had. But it strikes me that at least half of these samples have very low amounts, but there are large

numbers of products out there with those very low amounts, and that you might be able to come up with some kind of a dose-response relationship if you could simply look at the number of products in each of those different--I think you did them by 5 percent--

DR. LOVE: But you're making an assumption that all these products are equal and that they have the same numbers and types of ingredients.

DR. CHASSY: I'll tell you what I'm driving at. I'm trying to get at something--there are a lot of assumptions here. I'm trying to get at something that gives us some feel for where we begin to see a dose-response correlation, because as it stands now, you have effects all across the board. But you do have fewer products with very high amounts of ephedrine alkaloids in them, and where you have fewer of those products on the market, you seem to have around the same number of cases of adverse effects reported, which suggests that there is a dose-response relationship, but it's hard to suck that out of these numbers. And I'm sure you've worried about that, but--

DR. LOVE: Well, I agree with you, but I think that it's a very difficult problem. You know, we have hundreds of products with potentially hundreds of ingredients in some of them. So there's not a standardized

product that you can compare. We do not have incidence of prevalence data. We don't know how large the population is at risk. We do not know what the true reporting rate of any of these adverse events are. And so it is a difficult safety issue that we are dealing with today.

DR. ASKEW: Dr. Fukagawa?

DR. FUKAGAWA: Yes, regarding your examples of the adverse events in which there were no or few apparent complicating factors which were very compelling examples of potential effects, yet in letters that we've received from Mr. Appler from the Ad Hoc Committee on the Safety of Ma Huang and from Mr. Shapiro at Bass and Ullman, who also referred to the 20-year-old from Florida, suggest that his situation was perhaps not as clear-cut with the presence of other compounds in his hotel room, et cetera, and the lack of toxicological reports or analyses.

Could you clarify that particular case as well as whether or not--

DR. LOVE: Actually, all of his blood levels for anything else were negative, and the coroner directly attributed it to the use of this product.

Now, where is the exception is this is the highest level of ephedrine alkaloids that we have analyzed in any product.

DR. FUKAGAWA: So these two comments from the other two groups are a matter of interpretation of the actual reports.

DR. LOVE: The reports that I have seen said alcohol blood levels, illicit drugs, et cetera, were all negative in that consumer.

DR. FUKAGAWA: Okay. Thank you.

DR. ASKEW: Dr. Hsieh?

DR. HSIEH: My comment will be concentrated on ma huang instead of pure ephedrine alkaloid. As a user of Chinese herbal medicine, I studied about ma huang. I read about ma huang in the traditional Chinese medicinal book. And I must say that, Dr. Love, your presentation is almost like a modern translation or modern interpretation of what was said about ma huang in the book. And in the book, for example, some adverse effect of ma huang was very explicitly described. For example, it says don't use it, don't overdose. In case of overdose, there will be excessive perspiration and exhaustion of vitality, and don't use it in the summer months, something like that.

So there are other things that--if you are taking them in totality, ma huang seems to be a consuming kind of drug, medicine, and, therefore, if you know how to use the ma huang as a medicine, it says that you should use it very

sparingly. And when you make your tea, you have to put it toward the end of the tea making. That means the extraction time should be as short as possible, something like this.

So if it is true that ma huang can cause the consuming type of effect, then it is consistent with the observation that more females or the young and the elderly are being affected. And in my opinion, based on the presentation that I've heard so far, I think the adverse effect of ma huang is greater than the effect of the amount of ephedrine alkaloids that were measured, because the analytical measurement is an underestimate of those compounds. And I think in addition to those compounds, there might be other things that have adverse effects.

DR. LOVE: I agree with you, and I would also remind you that the other thing that's important here is there can be distinct racial differences in genetic metabolizer phenotypes that may well be different in an Oriental population from those that we see in the United States, as indicated by the information from Dr. Woosley, and would affect the safety of this product.

DR. ASKEW: Dr. Hsieh, for those of you who didn't see it, was looking at a book on, I presume, Chinese medicine. Can you give us the title of that, just for curiosity?

DR. HSIEH: Dr. Fong and Dr. Hui can translate it better. It's called pen sow pei yow (ph). It's translated as "The Concise Summary of Chinese Pharmacognostics." This book was written, was complied about 200 years ago, and it compiled information accumulated through the centuries.

So ma huang is a very well known basic Chinese medicinal herb, and as pointed out by Dr. Loeb, it was never intended to be used as a food. It has to be prescribed by health care professionals, not to be chosen by consumers. That was very clearly indicated in the book. I think Dr. Hui and Dr. Fong can correct me.

DR. ASKEW: Thank you for that perspective, Dr. Hsieh.

Dr. Jasinski?

DR. JASINSKI: Dr. Love, I liked your presentation, and I thought you were very scientific and very precise and very intellectually honest, and I want to go back to one of the things that you said, two points that you made, which basically bother me about this whole business, and you really brought it home.

One is--as I think Dr. Woosley said--everything that's there in the adverse events has been known for a long time. It's seen with cocaine, with amphetamine, and with ephedrine. And you point out that you can go back to the

1930s and you'll find case reports in the literature knowing this.

The difficulty that I have is: Is there a crisis and a real public health problem, and to what extent is there? Because as you pointed out, when you started this adverse event system, you went from a passive to an active system where you began soliciting cases, set up the ephedrine hotline, and I saw some of the other things in here, looking for cases, send me your sort of cases.

Once you do that, then it changes the ground rules, and that's one of the things you don't do in epidemiology, is go from a passive to an active system.

DR. LOVE: This is still a passive surveillance system. An active system would be where you do an actual case cohort or other type of study where you need a defined product and a defined--

DR. JASINSKI: Yes, but if you go out asking for people to start sending you cases and publicizing it--

DR. LOVE: But we do that for all dietary supplements. We're part of the MedWatch program. What happened, to give you the historical perspective, is in 1993 the Center for Food Safety was reorganized, and the Office of Special Nutritionals was created. And we saw that these occurred, and we decided to monitor and track all of them.

In June 1993, FDA initiated MedWatch, and dietary supplements were included with that. And so we've actively collected every adverse event that has occurred with every special nutritional product.

Now, we have publicized our safety concerns on a number of botanicals and other types of products, and these have gone up, too. But the overwhelming majority of what we see is ephedra.

DR. JASINSKI: I'm not arguing with that. I'm talking about the relative incidence over time and to what-- I mean, you're showing this increase, and how much of this increase is actually an increasing showing that we're getting a growing public health problem that's going to project, or how much of this increase is related to the change in the way you've done things in publicizing this and asking people to report in?

DR. LOVE: Again, you can't talk about it in incidence or prevalence. It's only a reporting rate, and we realize that there can be reporting bias.

DR. JASINSKI: But you show that graph of reporting--

DR. LOVE: But without a system to collect this, you don't have any of these. And I think the Texas experience as well as the other states is, when they have a

system that the consumer or health care professionals can report these, they start seeing a lot of adverse events reported because people do not know how to report these things.

DR. ASKEW: We have a number of people that have been patient in waiting to comment here. Dr. Potter just indicated he has something directly related to what was just said. Go ahead, and then we'll get back to our order.

DR. POTTER: Thanks. Lori, I think we could get at this question by looking at the rate of change in reporting for the other nutritional supplements versus the rate of change in ephedrine, just sort of standardize it over time to accommodate changes in methodology.

DR. LOVE: But what you also need is to know how much of a market this represents, and we do not have that information; how the market share is changing with these products, we know that they're increasing, but we do not know how much; who is exposed; how often, et cetera.

I agree that there are reporting biases in our systems, but there are also probably under-reporting also at the same time.

DR. ASKEW: Dr. Woosley also wants to comment directly on this issue.

DR. WOOSLEY: Directly on that issue, I think

these are problems with the reporting system. It doesn't bother me a bit--I mean, we don't need to know how big this problem is. There are at least 24 deaths. I mean, if there was one death, that's all it takes. Why are we worried if it's an epidemic or a crisis? It is a serious problem if one person dies, and I think clearly more than that have died.

DR. ASKEW: Let's go back to our order now. Dr. Katz has been waiting patiently to comment over here.

DR. KATZ: Just a quick clarification. What is the major metabolite of ephedrine? Is it norephedrine?

DR. LOVE: Well, it's norephedrine, but it's commonly called phenylpropanolamine. And, actually, if you look at the scientific literature in the United States, the marketed product phenylpropanolamine is a racemic mixture. But worldwide that's not true, and they talk about D and L forms of PPA now. In the body, it's the natural form of norephedrine.

DR. KATZ: And the final question is, the table above that, when you had adrenergic activity of different agents, the last one, is that supposed to be norephedrine or is that norepinephrine?

DR. LOVE: That is comparing it with norepinephrine, which is your classical catecholamine.

DR. KATZ: Thank you.

DR. ASKEW: Mr. Guzewich?

MR. GUZEWICH: I discussed my problem I am going to raise here with Dr. Yetley, and I hope that she can help me on this one, at some point bail me out. I'm a food regulatory person, and I think about food safety issues, and I have been trying all day here to put this in a food context. This is a Food Advisory Committee to the Center for Food Safety and Applied Nutrition, and I realize that because of its relationship as a drug why the panel is made up the way it is, and why the discussions have gone the way they are. But I'm still thinking about this product as a food not as a drug. And I come with baggage in that regard, just like people come with baggage on drugs, I guess.

In the context of food safety, I have to go for analogies like people go for analogies in drugs. My analogy is the GRAS list, which I know doesn't apply here under the law, exempts it from the GRAS list and so on. But I think about a substance that's going to be in food has to have a record of safety. And on the GRAS list, there's many compounds that were on the marketplace long before FDA had regulatory jurisdiction over such things, and those are allowed to be still in the food supply because many decades or centuries of experience with those products has shown

that they're safe, and so products can appear on this GRAS list and can be food ingredients.

I don't think this product would qualify as GRAS. I don't think this product could even come close to GRAS if it was being contemplated that way.

What I do know is that when consumers go into a store to purchase food, they know or they like to think that that's a safe product. They like to think that they can take that product at almost any quantity--I mean, we realize if we eat too much of some foods, we can get sick from them or we can gain weight or we can--whatever. But by and large, people think food is safe. They can go to the marketplace. They can select among the thousands of choices they can make, and they can consume that food at whatever rate they choose to consume that food, and it will be safe, and that's part of our free market economy.

Thinking of it as a food person and hearing all the comments that everybody made today about these adverse effects, I don't think this thing cut the bait when it comes to food.

DR. ASKEW: Okay. Dr. Ricaurte, you had a comment.

DR. RICAURTE: My question was already addressed. Thanks.

DR. ASKEW: Thank you. We'll go to Dr. Clydesdale next.

DR. CLYDESDALE: Thank you very much, Dr. Love. I just want to make sure I'm not misinterpreting it. The total ephedrine alkaloids in the various products, those products really do vary from 0 to 25. Do they? I mean some of the products.

DR. LOVE: Right. Well, actually, some of the levels are even higher than that if you look at the--there is considerable range in the pattern of individual alkaloids as well as the total ephedrine alkaloids. And as I indicated on the products where we had multiple samples from a single product from a single manufacturer, there could be considerable range, too, and that probably depends upon what their source of ephedrine alkaloids is, whether they've reformulated or other things that potentially interact.

DR. CLYDESDALE: I'm sure you wouldn't have the answer to this, but I guess I would just like to bring it out as a question because we are worried about safety. Is there any standard that the quality control of the industry aims at when they make these products? I mean, apparently it isn't ephedrine because that varies from 0 to 50 or whatever. Is there anything else that when they mix and match these products that the industry aims at when they do

an analysis to make sure that they're selling the consumer an equal product every time they sell it?

I'm sure you can't answer that, but I guess I just wanted to raise that because it seems to me--again, I'm from the food area, and if you say you're giving the consumer a product, it's supposed to be the same product every time, or close to it.

DR. LOVE: Again, I will defer that to the representatives from industry.

DR. ASKEW: We might be able to ask that question of one of our public hearing speakers. Keep that in mind, and if an appropriate one approaches the microphone, why, we'll collar them on that one.

We have Dr. Ziment, Dr. Wang, and then Dr. Bruner. Dr. Ziment?

DR. ZIMENT: I was just going to comment about the overall usage of these drugs, and I've got a report here of a "PrimeTime Live" television interview in which the CEO of the Los Angeles company that manufactures Herbal Ecstasy said that his firm alone sold 15 million units of this product. The amount sold in this country must be absolutely enormous. Is there any further details or extrapolation from this type of information to guess what the market is?

DR. LOVE: I and I think generally FDA do not have

this data and will have to defer to industry.

DR. ASKEW: Dr. Wang?

DR. WANG: Thank you, Dr. Love, for a very informative presentation. I have a couple points of clarification I'd like to ask you.

In your table where you have total ephedrine alkaloids in consumer products, are these products combination products, combination products with ingredients that may be stimulants?

DR. LOVE: The majority of products that we see, as Connie indicated in the market survey--and it's also true for what we see where there's adverse events--are multi-ingredient products and are not single-ingredient products.

DR. WANG: So they are all multi--

DR. LOVE: The majority, the overwhelming majority are multi-ingredient products.

DR. WANG: And these ingredients made in combination, they are cardiovascular stimulants and central nervous stimulants--

DR. LOVE: Some of them can be, such as the sources of caffeine. Some of them we probably don't know.

DR. WANG: Which you did not analyze, that the lab only analyzed total ephedrine alkaloid?

DR. LOVE: We were looking at ephedrine alkaloids,

and there were some that also looked at some of the caffeine levels.

DR. WANG: Thank you.

DR. ASKEW: Dr. Bruner?

DR. BRUNER: Thank you. This kind of segues into one of Dr. Clydesdale's points. You did mention, Dr. Love--and thank you again for a great presentation--that there is a considerable range in dosage of the ephedrine alkaloids. But in your report of adverse events, the preponderance was in weight loss and energy products, and I just wondered if any correlation was made between the dosage of the ephedrine alkaloids taken for, say, weight loss versus ergogenic or stimulation was done.

DR. LOVE: No, we didn't do that. But if you actually look at the types of ingredients that are in these products, except for the ergogenics that can have a lot of the amino acids and some of the protein powder type things, the types of ingredients are very similar. That was also pointed out in the market survey that Connie Hardy presented. So the numbers and types of ingredients are similar. What differs is kind of their claimed use, except where you see these protein powder type products in the ergogenic/body building products.

Now, there are also capsule/tablet products in the

ergogenic that would be more similar to the weight loss products.

DR. ASKEW: Dr. Potter?

DR. POTTER: Dr. Hsieh indicated that perhaps it's the dose that's the toxin rather than the product, and Dr. Woosley indicated that maybe there's a poorly predictable individual response that makes it very difficult to predict what dose might be toxic. And I wonder if in your magic text there there are some hits that would help us come to some sort of a general sense of where we might find a safe level for some consumers even if we can't find a safe level for all consumers.

DR. LOVE: Well, as I indicated, the median and the mean doses are quite low, both for total ephedrine alkaloids and for ephedrine itself. And if you look at specific cases where attribution is pretty clear, including some of the case examples I showed, those levels for ephedrine range in the 1 to 5 mg range for that individual on that product that they were consuming at the time they had their adverse event.

DR. ASKEW: Dr. Hsieh would like to respond to Dr. Potter's question.

DR. HSIEH: According to the Chinese traditional medicinal literature, ma huang is a potent, fast-acting

medicinal herb. And in the prescription, it is used very sparingly. Usually the dry product not to exceed 3 grams of dried ma huang herb per recipe. Usually it does not exceed that.

DR. ASKEW: Thank you. Dr. Fong?

DR. FONG: Yes, this is a follow-up of Dr. Wang's and Dr. Bruner's question. There are two questions--not questions but clarifications I would like you to answer if you can.

Number one, in regard to the fact that the adverse event you're seeing and the common thread being the ephedrine alkaloid, which I don't dispute, the question I have is: Is there any way one can tease out the adverse events associated with ephedrine alkaloids plus caffeine? When you combine those two, as I understand my little bit of pharmacology, you get a synergistic effect on the cardiovascular system, particularly for a person like me. That's number one.

Question number two really pertains to the clinical trial on obesity. You went to great length giving us the adverse events, but I have not seen any data to what those doses are to effectively reduce anybody's weight.

DR. LOVE: Actually, that information is covered in your briefing book under the safety evaluation that had

been provided to the committee last fall. You will find all the data in the references there.

The comment on the combination is the majority of these products appear to have a source of caffeine, and the other problem is caffeine is so pervasive in our environment from colas, coffee, and other food sources that that would be something very difficult to control, but we know from controlled clinical trials that it certainly can have interactive effects. It has been shown with caffeine and ephedrine and it's been shown with caffeine and phenylpropanolamine in controlled clinical trials that it can have interactive effects, sometimes synergistic effects.

To go back on the response to the dose-response, I would just like to make a comment that we have two different patterns of injuries that can occur, and it's probably more likely that you're going to be able to decide on a dose-response on those adverse events that appear to be more acute than those that are more chronic, such as the myopathies and cardiomyopathies, and maybe Dr. Woosley can comment on that. But those patterns are consistent with what we know on other amphetamines and cocaine, et cetera, and they can be at quite low levels of chronic use and appear to be the result not of an acute toxicity but changes in receptor sensitivity, the calcium channels, potassium

channels, et cetera.

DR. ASKEW: We have two people that want to comment, Dr. Dentali and Dr. Hui. But, Dr. Woosley, would you want to respond?

DR. WOOSLEY: Just to quickly say that I think you're probably right, although if you look at all the drugs that affect the sympathetic nervous system, there is a very poor dose-response relationship in a population, beta blockers, all the drugs that effect the autonomic nervous system, and it's because of the factors I mentioned earlier. But the predominant cause is the variability in our own endogenous physiology.

DR. ASKEW: Dr. Dentali?

DR. DENTALI: Just a follow-up to Dr. Fong's questions. I guess where I'm going is the subset of products that are herb, herb extracts, containing amounts of ephedrine alkaloids that would be in compliance with the October recommendations. I was really glad, Lori, to see the--I think you did mention that it was maybe only 40 percent out of the adverse reactions that were ephedrine alone compared to ephedrine and caffeine combinations. I was wondering--

DR. LOVE: I didn't say that. The majority of the products appear to be combination products.

DR. DENTALI: Are combinations. It occurs to me that certainly simply not allowing combinations, although caffeine is prevalent, we don't have to allow it to be put into the same capsule or tablet. I'm wondering if the data has been looked at limited to combination--exclude the combinations, limit it to herb and herb extracts, limit the dose, limit the duration if we have any indication of what sort of safety problems we're facing there.

DR. LOVE: Those are comments that are before the committee. I remind you that 35 percent of the adverse events are on less than a week's use, and 14 percent are with the first use or first day of use.

DR. DENTALI: Those would also be with caffeine?

DR. LOVE: That's true, and it would need to be evaluated.

DR. DENTALI: Thank you.

DR. ASKEW: Dr. Hui?

DR. HUI: I just want to second Dr. Woosley's comment. I worked with beta receptors for about 8, 10 years, working with beta receptors, tachyphylaxis, up and down regulation, and obviously there's a lot of variability in the response, and a lot of patients who cannot tolerate caffeine would probably have a lot of trouble tolerating ephedrine. And based on your discussion, it doesn't seem

like there's a safe dose. You are probably one of the few people who really have looked at this data. What do you think would be a safe dose?

DR. LOVE: That's for the committee to discuss.

[Laughter.]

DR. LOVE: That's why we have you here.

DR. ASKEW: Dr. Croom has his hand up first. Then we'll go to Dr. Jasinski, Mr. Ford.

DR. CROOM: Do you see anything--I'm trying to go through, and part of the reason we asked for uses, we can see we've got traditional Chinese use short term for colds and asthma, and, Dr. Love, what I'm wondering is: It appeared from when I looked through the individual cases and your bars, these do not appear associated with several adverse events. Is this right? When we look at the cases of when people are using things here and having adverse events with ma huang, is it a low incidence of adverse events, especially serious, where we're talking about death, myocardial stroke, hallucinations on the CNS, something like that?

I'm not seeing products show up that are being sold for cold, asthma, Chinese traditional medicines.

DR. LOVE: That's because 92 percent of the products are weight loss and energy. The other--

DR. CROOM: But are there serious adverse events--in looking through the cases given me, I did not see serious adverse events--I'm looking for risk factors, okay? I do not see that in these case reports. Something's different there.

DR. LOVE: There are very few reports that we've received of adverse events on products marketed for traditional use in traditional forms. Now, whether that's because we haven't received the reports or there's truly a low rate of reported adverse events, I can't say.

DR. ASKEW: We're going to go to Dr. Jasinski, Mr. Ford, and Dr. Inchiosa, and then we're going to have to move into the public comment section of our hearing. Dr. Jasinski?

DR. JASINSKI: I've given ephedrine to people when I was with the Federal Government. I have given both injectable and oral ephedrine, and there are systematic dose-response curves which are quite reproducible. I've also infused cocaine, and I have given subcutaneous cocaine, and you get nice dose-response curves. The difficulty is that what happens is you'll get cocaine users who will be using cocaine, and they show up in the emergency room with cocaine and with other stimulants, but predominantly now recently with cocaine. They'll look just like this.

They'll have an EKG that looks somewhat abnormal. Their enzymes will go up. They go up into the CCU overnight, and the next day they're fine and they're discharged, and people start complaining about them filling up the CCU and the house staff of university hospitals find them to be very uninteresting cases because the people want to split the next day. Then they'll go back to using cocaine, and they won't show this.

So this issue I think is very important. There are effects which are pharmacologically predictable in people, and there are effects which occur--some of those cardiovascular effects which occur at times and for reasons we don't know and which are not dose-related and may be due to--sometimes you see them with very low doses and may be due both to state and trade sort of issues.

DR. ASKEW: Mr. Ford?

MR. FORD: There were a couple of questions asked about industry practices and statistics that I can more or less answer. We don't track the sales of individual products as well as maybe we could, but as far as ephedra products bought from health food stores, the figure that we have used is about a million and a half doses per day, and that's just from the health food stores. Of course, the vast preponderance of the products that are involved in the

more serious injuries do come from non-health food store sources.

Secondly, the question was asked: What will we accept as a percentage of label claim of an ingredient? And in our true label program, which is a random testing and label registration program, we will accept from 90 to 110 percent of label claim, which I believe is what the USP standard is. But that's what we use in our program when we do the random testing.

I just also wanted to add or raise a question. What started all of this was the adverse reaction reports. That's how we first started meeting with the FDA because they had concerns about the frequency with which these sorts of events were being reported. And we see here that the data from the controlled clinical trials, which is not these adverse events, indicate that a significant proportion of healthy individuals can experience adverse effects with the use of ephedrine. I'm certain that's quite true. But there must be a pattern with respect to dosage that does emerge, because listening to Dr. Davidson this morning from the Chicago Institute for Clinical Research, he indicated that a very, very small percentage of the injuries that are being reported occurred when the dosage was at approximately what the industry is calling for, the 15 per dosage and 60 a day.

I think he used a figure of over 90 percent of the injuries are with dosages above those levels. So there is some consistency that at least we see.

DR. LOVE: And may I ask how he determined that, how he determined what dosage levels were and what a low dose was? Because he did not state that this morning.

MR. FORD: He stated that in an interview--he reviewed the reports that were furnished to us.

DR. LOVE: And on what basis did he decide a low dose, and what was the low dose? Because I didn't hear it stated this morning.

MR. FORD: From the averages that he came up with from looking at the reports, Lori, 187 of the reports.

DR. LOVE: So you're going from what the label claims and not what an analyzed value is?

MR. FORD: No. I think that this exercise is to determine, if ephedra is going to remain on shelves in products in health food stores, what is an acceptable dosage for that ephedra? Or is it not acceptable at any rate? And I don't understand why there's not a pattern that emerges that the agency can talk about that speaks to a dosage level where the injuries drastically drop off.

DR. LOVE: We've told you where the injuries are today. From the information--

MR. FORD: There's no way to determine a safe level.

DR. ASKEW: Dr. Kessler would like to address that point?

DR. KESSLER: What I found interesting--and maybe Dr. Love can comment on it because she has helped teach me, teach all of us. When I first became aware of the Florida case, that was a high, relatively high dose of ephedrine, it was an acute event, like you, was saying, gee, that's a high dose of ephedrine. What surprised me a little was when I started looking into with Dr. Love the second case. You have many cases in your report, but the two that I focused on, the case of the 24-year-old Tufts student. That seemed to be at a much lower dose, and the kind of cardiac pathology, the myocardial necrosis, seemed to be evidence of chronic toxicity consistent with the sympathomimetic use.

I guess that, what I understood from the pathologists, was that both types of pictures are in the literature, both the acute event at the higher toxicity--and maybe that is a dose response, but even at the lower levels, the George Karisis(?) case, there was harm.

DR. LOVE: I think both can occur, and I think that you have to remember that it's well quoted in the scientific literature that there are no good correlations

between particular blood levels and particular effects, including adverse effects and in some cases, pharmacologic effects with particular doses of ephedrine.

When you get to a high enough dose, you're going to see a dose-response, and at a high enough level, everybody is going to develop toxicity. Where you have a problem is at the bottom end where all of these other factors influence what that level is going to be and how you're going to respond. And there are not good data on that.

DR. KESSLER: When you say not good data, what do you mean? Not complete data--

DR. LOVE: On how individual receptor density affects it, the gender responses, the effects of hyperdynamic states. The data from obesity is done in obese patients which are known to be less sensitive to sympathomimetic agents. So if they're developing a--

DR. KESSLER: But a lot of them have high blood pressure.

DR. LOVE: No, those were all excluded from that clinical trial. Those with risk factors or hypertension, et cetera, those confounders were excluded from that clinical trial. So that's not true, and that is what you're dealing with in the normal population.

DR. ASKEW: There has been very good discussion on Dr. Love's presentation, and we need to get to our public comment section. We have Dr. Inchiosa, Dr. Ziment, and Dr. Ricaurte that want to speak yet.

If your comment can be held until the discussion tomorrow, we'd like you to do that. If you really would like to bring it out at this point and make it quick, we'll do that. Either of you three want to comment at this point, or can you hold it for tomorrow?

DR. INCHIOSA: I would like to comment about the dose aspect.

DR. ASKEW: Please go ahead.

DR. INCHIOSA: I know there have been a number of comments made. Dr. Woosley described receptor differences, age differences, but even in just the small amount of data we have in front of us in terms of the pharmacokinetic data, it shows that--and I've seen a larger range than this, but this pharmacokinetic data shows a four-fold difference in half-life, half time of elimination. The data I know from another source is five-fold.

So, therefore, when you talk about a dose, an assay dose in a tablet of 15 mg, that's equivalent to a 75 mg tablet in another individual in this normal range. So, therefore, one person taking a 15 mg tablet per day, or

whatever the dose would be per day, is going to have a certain blood level. Another human being in our normal distributed population will have five times that blood level, and that's one of those physiological differences that exist, but that does confound the issue.

And one other point I feel which I don't think was made, although Dr. Woosley alluded to interactions, but it impressed me that in many of these preparations they are taken in scoopfuls of large amounts of organic material which is going to compete with metabolism in the liver. And so I think that's going to change half-lives even more.

We've mentioned beta blockers or beta receptors. Beta blockers in the human population have a 20-fold difference in half time of elimination. So you give everyone the same dose of propranolol in this room and blood levels will vary by 20-fold. So that there's an enormous individual effect which will confound the ability to see in moderately small numbers a pure dose relationship.

DR. ASKEW: Thank you for those comments.

We're going to move now to the public hearing portion. This will be our last session for today, and Dr. Larsen will introduce our speakers.

DR. LARSEN: I want to emphasize that Dr. Love will be here tomorrow. You'll get another shot at her, I

guess, tomorrow.

The first public hearing speaker for this session--if I've got my notes straight at this point, at any rate--is Ms. Mary Miller from the Alternatives to Violence Project in the Delaware prisons from Dover, Delaware. If you would repeat your name and affiliation to make sure it's on the record and that I've got it right, and anyone that may have supported you in coming here, and you have seven-and-a-half minutes.

MS. MILLER: Thank you. I won't take all that time.

My name is Mary Miller, and I am the coordinator of the Alternative to Violence Project in Delaware. We work in four Delaware prisons, and we're all volunteers, and we work with inmate trainers teaching inmates how to deal non-violently with the conflict in their lives. We probably all could learn how to do that ourselves.

I am reading a letter from one of the inmates who coordinates our project in a prison in Delaware. He is serving a six-year term. He's been in for about three-and-a-half years, and I don't normally get involved with cases of the inmates that we work with. We see hundreds and hundreds and hundreds a year. But when the ephedra warning came out in April from the FDA, he called me and he said,

"That's the stuff I was taking before I was arrested."

So this is his letter. He couldn't be here. He would have liked to have been.

[Laughter.]

MS. MILLER: So I'm bringing his regrets for not being here, and also his regrets about taking ephedrine. His name is John Larson.

Dear Committee Members: I would like to share with you the adverse effects that ephedrine has had on my physical well-being on my life.

I am 36-year-old male, who currently has served 41 months on a six-year sentence.

On December 24, 1990, I was hit head-on by an uninsured driver. I was seriously injured and spent almost a week in the hospital as a result of these injuries. The following June I was involved in another serious accident.

I was under the rehabilitative supervision of a doctor, and I was having extreme difficulty with my rehabilitation.

At this time, I had been in recovery for 3 years from an addiction to methamphetamines that had lasted for 8 years. I had a brief bout with the pain medication I was on as a result of the injuries I had sustained in the auto accidents. I voluntarily placed myself in a drug rehab

center where I successfully completed the program.

After my release from the drug rehab center, I tried to return to my line of work. My partner and I had a fairly successful kitchen and bath installation business. This type of work is extremely physical, and I was unable to keep up because I had lost a lot of weight and strength due to my injuries and the bout with the pain medication.

I went to several health food stores where I explained that I was a recovering addict and did not want to compromise my recovery and that I was easily fatigued, weak, and was having a lot of trouble keeping up at work. All of the people I talked to suggested that I take ephedrine in different forms. I did this. At first my energy level rose, and I was able to keep up at work. However, it did not take long before I was unable to control my intake of ephedrine. I was soon ingesting 1800 milligrams of ephedrine HCL per day, along with many other natural forms of ephedrine. I began to have hallucinations, paranoia, violent outbursts. I was unable to differentiate right from wrong. I did not make the connection that the ephedrine was causing these problems until I was incarcerated and it got out of my system. I honestly thought I had lost my mind.

I was subsequently arrested and convicted for my bizarre and violent behavior even though I have no prior

history of this behavior. Nor have I shown any signs of this behavior during my past 41 months since I have been incarcerated. I have lost my home, my business, my freedom, my children, my life as I knew it.

As a recovering person, I value and need to be accountable for my recovery. However, in doing some research on ephedrine, I have found out that it is chemically similar to methamphetamine and therefore could have caused a relapse response in me. It seems to me to be cruel beyond words to give a person in recovery something chemically similar (ephedrine) to the drug he is in recovery from with no warning as to the possible adverse effects it may have on him; something for which there may have been many documented cases, including psychosis, and then hold him responsible for the adverse outcome, incarcerate him for trying to improve on poor health and following the advice of natural health professionals.

I now suffer from almost constant headaches, blurred vision, high blood pressure, difficulty concentrating, bouts with severe fatigue and irritability, and a number of other problems which I did not have prior to ingesting large amounts of ephedrine.

I'm sure it would be easy for you to dismiss this as a ploy by another convict. However, I am almost finished

my sentence so that is not a factor. This is all documented in the record of my case, including statements made by the victim which clearly state that my behavior became bizarre and violent as a direct result of ingesting ephedrine.

How do I begin to rebuild a life which has been destroyed as a result of this product? How do I replace the years which I lost for my children who were 4 and 5 were incarcerated and who are now 8 and 9? How do I make up for something I had no control over?

I implore you to do something about this product before more lives are shattered. This product is certain to destroy the lives of many recovering methamphetamine or amphetamine addicts and the lives of those who are predisposed to this addiction who are unaware of the dangers this product poses to them.

Thank you for your time. Sincerely, John Larson.

That's it.

DR. LARSEN: Thank you.

We have time for one question from the committee. Dr. Dentali, did you have a question?

DR. DENTALI: I just want to point out that it appears we're dealing again with ephedrine HCl and not an herb or an herb extract. You know, I guess time and time again I bring that up only because I'm concerned with the

subset of products we have here that may be cruder or crude, simple compounds, crude extracts, or extracts that would comply with the October recommendations.

Thank you.

DR. LARSEN: Thank you.

The next speaker is Mr. Anthony Young, general counsel for the National Nutritional Foods Association, Washington, D.C. If you can repeat your name and affiliation so it's clear for the record.

MR. YOUNG: Thank you. I'm Tony Young, and I'm appearing here as general counsel to the National Nutritional Foods Association. NNFA is the trade association of manufacturers and retailers of dietary supplements. Many of our manufacturers distribute legitimate dietary supplements containing herbal ephedra or its extract, not the chemical salts of ephedra. These dietary supplements are sold by thousands of natural food product retailers nationwide, many of them NNFA members.

The products our industry sells are dietary supplements, which a federal law defines as a specific subset of food. When I said that to the Ohio Board of Pharmacy two years ago, just before that law was to be passed--actually, I think it was between passage and signing by the President, they said no, ephedrine is a drug whether

it is herbal or it is a chemical salt, and they determined to regulate it that way.

This committee seemed to be struggling this morning with the same issue. Herbal ephedra is a pharmacologically active compound, and how it can be labeled and used in dietary supplements is what we ask you to address.

NNFA is co-author of and endorses the position statement provided to you this morning by American Herbal Products Association President Michael McGuffin. We retained Dr. Michael Davidson to review the adverse event reports, and you have his opinion on that subject. With respect to his low-dose conclusion, he went through the dosage amount, the per serving amount information provided to the committee last year, and determined which products contained 15 mg or less per serving ephedra alkaloids. He then went back and looked at the adverse reaction reports in the materials you have to determine how many had been associated with those products.

He excluded one product--Nature's Nutrition Formula One, which FDA evaluated to have a very low amount per serving, which we understand is just contradicted by the label for that product and what has generally been known about the amount of ephedra that was contained in that

product. We think the analysis was an anomaly.

The Dietary Supplement Health and Education Act of 1994 recognizes warnings on labels and labeling. Communicating to consumers about the use and hazards associated with these products should be priority number one in any recommendation on ephedra that evolves from this Advisory Committee. Connie Hardy's presentation provides convincing evidence of the need for clear label recommendations. For example, the need for consistent expression of ephedra content is obvious and has been urged by FDA to us and by us to our--and the other associations to our members for some time. You can require it by determining that it is simply not safe to market ephedra products without disclosing the amount of ephedrine equivalence, expressed as a ephedrine equivalence, per serving. It's not safe because consumers and health professionals need this information to safely use the product and to respond to adverse reactions.

The majority of our industry will respond promptly to changed labels and to lower doses in response to recommendations from this committee. Major retailers will persuade their suppliers to promptly comply. Major multi-level companies have told us that they will also comply.

Finally, the major trade associations are prepared

to move promptly to prepare an ephedra information brochure to be made available to consumers. Such a brochure could cut through the labels, the labeling, and the sales talk that may accompany these products. We would be pleased to work with a subcommittee of the Special Working Group on this and to put a tight timetable on drafting and then circulating and making available that kind of information to consumers.

We would hope that addresses the kind of issue that Mr. Guzewich raised earlier, that consumers may believe these products are simply good. We want to get full and complete information to consumers.

In summary, we endorse and we look for responsible labeling and formulation of dietary supplement products containing ephedra. We agree that full information should be made available to consumers.

Thank you for your consideration of these comments.

DR. LARSEN: Thank you. I believe it was your letter that I was informed I overlooked another speaker. Were you able to get hold of Dr. Graham Patrick or not?

MR. JONES: No, I'm not associated with Dr. Patrick.

DR. LARSEN: Okay, I'm sorry. It wasn't your

letter then.

Does anybody on the panel have a question for Mr. Young? Dr. Ricaurte?

DR. RICAURTE: Just a quick question. I guess my concern would be that as you make information available to consumers that this is a compound that can produce CNS stimulation, that can reduce appetite, many consumers are going to view those bits of information as positive features, and indeed may tend to use more of the product than recommended on the label. My question is: How would industry regulate misuse of the compounds?

MR. YOUNG: I think that goes to something, I think, that Connie Hardy described as "stop here" labeling, "Do not take more than..." and I think we need responsibly to deliver that message more firmly and describe the kinds of effects that might be associated if the consumer goes beyond.

I think all we can do is provide as much information as possible.

DR. LARSEN: We have two more questions. I guess we've got a couple minutes. Dr. Hui and--who was the other one?

DR. HUI: Is there anything similar in the food or dietary supplement products anywhere close to what we are

dealing with with ephedra-containing dietary supplements that the industry has to circulate a brochure?

MR. YOUNG: No. I think this would be the first start. Our association has circulated information on other materials from time to time, but this would be something that we would reach beyond our trade association and try to get everyone to make it available. It would be kind of a product information type brochure.

DR. HUI: Aren't we talking about really a fine line between what is food, dietary supplement, and drug?

MR. YOUNG: Well, I think--you mean are there other ingredients that are like ephedra? Niacin. Niacin is a dietary supplement, and it is also a drug.

There certainly are other materials that are regulated as dietary supplements in one context and as drugs in another context.

DR. LARSEN: Dr. Applebaum?

DR. APPLEBAUM: Thank you.

Mr. Young, I hope I don't use the wrong terminology, but in regard to Dr. Davidson's presentation, am I correct in saying that he identified a safe dose at 15 mg?

MR. YOUNG: His statement, I believe, states that he found that there were lower effects--that the effects

were not as frequent, and I think he said he only found one serious after doses of 15 and below.

DR. APPLEBAUM: Okay. I think he said two serious, but we won't--

MR. YOUNG: Okay. You have it. I do not have it in front of me.

DR. APPLEBAUM: But his assessment is based on a review of the reports; correct?

MR. YOUNG: The 618, yes.

DR. APPLEBAUM: My question then is: Does the association or any of its members have any safety data themselves that could be included in this discussion that we as members of the Food Advisory Committee could use to come to some type of conclusion?

MR. YOUNG: No, I think the association has--first of all, Dr. Davidson talked about doing a dosage study and doing a follow-up on it or the following of a thousand patients. I think the industry in general has relied upon the use of ephedra generally and safety studies or other studies that have been performed on ephedrine hydrochloride.

DR. LARSEN: Thank you. We're going to want to move on, but Dr. Clydesdale did have one question. After him, we'll move on to the next speaker.

DR. CLYDESDALE: This is just a follow-up. Was

that value that Dr. Davidson came up with of 15 mg, was that a label value or an analytical value?

DR. LOVE: Can I clarify? I think that that's based on the market survey, and it's not the analytical values of the consumer samples themselves.

DR. CLYDESDALE: Okay. So that value could have the variance that was shown in the samples that you had?

DR. LOVE: The data that I gave were on the actual consumer samples. The data that he is quoting is from the market survey, which was meant to be a capsule in time, one product, one time.

DR. CLYDESDALE: So it was not an analytical value.

MR. YOUNG: We used Tab C--

DR. LOVE: Analytical value but it's not what the consumer used.

MR. YOUNG: Right. We used Tab C from last year's material to determine that information.

DR. LARSEN: Thank you, Mr. Young. And I might remind you we do have our two industry liaisons at the table. So any of those questions can still come out tomorrow during your committee discussion, and certainly if they don't have the answer, they have access to their colleagues to get the answers.

DR. CROOM: Lynn, let's add that Tab C did have analytical data if that's what they used, so I think we should find out--

DR. LOVE: But that is the market survey, which was randomly collected samples to show what was on the marketplace. Those were not the consumer-related samples.

DR. CROOM: And does anybody have that consumer-related sample to guide on this dosage?

DR. LOVE: I was pointing out the data that I was giving you was consumer-related samples.

DR. CROOM: But not to serious adverse events--

DR. LOVE: Yes, there are serious adverse--

DR. CROOM: No, I mean related by dose. Related by dose. Just to give a parallel for this argument--

DR. YETLEY: The plot that Lori gave, which I think is creating the confusion, was a plot in which we had access to the sample that the consumer was taking at the time they reported an adverse event or injury, and we analyzed that sample.

What was in the market survey was we went out to the marketplace and bought a sample of a product, which in some cases may have been the same product that the consumer reported taking. But I think Fergy's point is right. We don't--the market basket sample and the consumer sample may

have varied, given the variability we have seen in some of these products. We had multiple data points.

DR. LARSEN: We're in the middle of the open public hearing. I know Dr. Kessler wants to make a comment. Let me ask a question of Mr. Prochnow, Dr. Dickinson, and Dr. Jones. Will the three of you be here tomorrow if we--I mean, I'm going to let this run and try to get you in today, but if we have to shorten it, you would be here? Okay. At least Dr. Dickinson says yes. Dr. Jones we will have to get in.

Go ahead, Dr. Kessler.

DR. KESSLER: Just on that last point, Mr. Young, we appreciate very much your statement and the willingness to work with us in trying to come up with the right answer, and I think everything you said makes a lot of sense. I just have one question, and that's the level that you talked about. If you look at Dr. Love's data--

DR. LARSEN: Can you get closer to the microphone, Dr. Kessler, please?

DR. KESSLER: If you look at Dr. Love's data, I guess what the median 50 percent of adverse reactions based on the label--

DR. LOVE: The median is going to be right through this level as the consumer used it. So 50 percent are going

to be less than that, 50 percent are going to be higher.

DR. LARSEN: Lori, Dr. Love, I think there is a mike right next to the overhead projector there, one of the lapel mikes. See if that will work so we can hear you on the system. You may have to turn the switch on on the box.

DR. LOVE: Is it on now? Okay.

We calculated the data two ways. We looked at data and looked at samples where we had information on how the consumer used the sample, which may have been different than the label instructions and was different in some cases.

The median, as the consumer used it, is right at this 25 mg ratio, meaning that 50 percent of the adverse events--and there are very serious adverse events in that--are less than that level and 50 percent are higher.

If you look at how it was on a milligram per serving basis, it's right up at the 20 mg level. Now, if you look at all of our samples, and we had about 60 consumer-related samples that were either the one that the consumer took or another one selected from another lot, same lot, post lot, at a similar time that the consumer used it, we had 60 samples, and, again, the median is about 20, for total ephedrine alkaloids. I didn't put the second slide in, but when you look at ephedrine in that, it puts it down in the 6 to 7 mg ratio for the median, quite low levels.

These are on consumer-related samples, and then the other slides I showed you, there was considerable product variability even within an individual product. We had multiple samples on about five or six different products for the different manufacturers, and they all show the same pattern of variability.

I think that is the point Dr. Kessler wanted to make.

DR. KESSLER: Just a question for Mr. Young, if you're willing. You had mentioned the 15 number, but I guess the question is: As this committee does its work and as the agency does its review of all the information, are you hard and fast on the 15? Or would you be supportive of working with the agency when you look at all this data and the way Dr. Love does it of trying to come up, if there is a safe level, with the agency and with the committee?

MR. YOUNG: I think we would work with the agency. Dr. Love's data, these are 36 cases that were analyzed as consumer samples, and I think we've heard about confounding problems in the analytical. We tried to rely on a different set of data. It is truly a different analysis of the information, but we would certainly be willing to work with the agency and to make Dr. Davidson available to work with the agency to try to develop that number.

DR. LARSEN: Dr. Dentali, is your question directed to Mr. Young? Okay.

DR. DENTALI: Well, it's regarding this graph here. The assumption is, again, that we're dealing with ephedrine and caffeine alkaloids. Is that correct? I mean, it's two groups. If we're going to look at setting numbers, we're looking at ephedrine alkaloids and ephedrine alkaloids with caffeine. I think there may be different levels of ephedrine alkaloids under those conditions that we might want to be looking at.

DR. LOVE: That could be true, but, again, you're going to have to control dietary and other sources of caffeine, too, as a risk factor.

DR. LARSEN: Thank you. I want to move along. Like I say, you'll have plenty of time for discussion tomorrow around the table. Dr. Love will be here. Some of the other folks will be here.

I want to put Dr. Dennis Jones on next to make sure that he gets his say in before he has to leave. Dr. Jones is the president of Fytoresearch, Incorporated, in Quebec, Canada. If you can repeat so we have your exact name, title, and so on, accurate for the record, please.

DR. JONES: This is indeed Dennis Jones, and I am president of Fytoresearch, which is a Canadian company that

researches, develops, and manufactures products containing ephedra herb. Currently that company and another associated company have 17 approved products in Canada. I am also associated with U.S. companies that sell these similar products as dietary supplements in the United States, and we do have offshore approvals, including offshore approvals for the indications of weight loss in several countries outside North America.

I assume everybody has got a copy of this, and, therefore, if they can't understand my accent, they'll be able to read what I was going to say anyway. My other affiliations and background are given on pages 6 or 7 of this document.

I had intended to touch on the inconsistencies between the FDA list of adverse events and other information that has become available in some detail. But I think that the FDA list of reported adverse events has been subject to a lot of criticism already today. Suffice it to say that I have some difficulty in associating a death with a product containing ephedra herb or ma huang when a toxicologist can't find any ephedrine or related alkaloids in the blood.

I also had accepted the regrettable case of Peter Schlendorf as being a legitimate case. It may still prove to be a legitimate case, but I gather that the autopsy

showed that there were pretty high levels of phenylpropanolamine which could not be explained by the compound he had taken. And there's also very little caffeine. There are a number of explanations for this, which I think the coroner and the toxicologist should be discussing.

There has been very little concern expressed about ephedrine or ephedra herb offshore. You already heard this morning from Dr. Ho there have only been two adverse events reported in Canada. I have been in contact with various offshore agencies. The Committee on Safety of Medicine, for example, told me in a letter, which is appended to this report, there have only been 22 reported adverse effects with the Do-Do tablet, which is an ephedrine/caffeine combination, in many years in the United Kingdom. They advise also that the inclusion of a particular suspected reaction does not necessarily mean it is being caused by the drug. They have no concern, according to a telephone conversation I had with them, about ephedra herb.

I should also add that a fixed ephedrine/caffeine combination based mainly on the work by Astrup and his colleagues has been approved for weight loss indications in Europe and is being touted by many as the safest and most effective treatment available. Danish data indicated only

86 reportable adverse reactions, which were defined as reactions which necessitate stopping the therapy, out of 9.6 million daily doses during a two-year period, despite relatively high dosage level, and particularly high dosage levels of caffeine.

In the United States, our market surveillance covers over 300,000 users of ephedra herb with a particular range of products and has failed to reveal any serious adverse effects. We have had occasional minor complaints, but these were generally associated with failure to follow label instructions--in other words, failing to start with a low intake and building up to a comfortable level--taking product at the wrong time, in other words, taking it too late and being kept awake at night--and these complaints did not occur in those who followed label instructions.

I must add that the products concerned are manufactured under GMP conditions to a strict specification, and we analyzed both incoming raw materials and the finished product for ephedrine alkaloids and alkaloid pattern. And it has to meet the specification. Also, those who sell this product have a larger information sheet and are provided for their own use with a 140-page monograph, which basically gives them all the information they need. It's a question of education.

Finally, neither the historical literature nor the more recent scientific literature contains reports of adverse effects, and this herb has been used worldwide for at least 5,000 years, in many cases in multiples of the dosage which are now normal in North America. Chinese reference works give an intake level which is sometimes six times the level that was recommended last year by the Special Working Group. It is also relevant in this context to mention that the Department of Health and Human Services did a two-year carcinogenicity study which came out absolutely clean. The only surprising result that came out was that high levels of ephedrine hydrochloride intake caused female rats to live longer.

The available data indicates that though ephedra herb shares some of the properties of ephedrine itself, it also possesses beneficial properties in its own right and is furthermore much better tolerated on an alkaloid equivalency basis. Some, but not all, clinical studies of ephedrine, mostly with caffeine in weight loss, have shown some minor side effects classified as clinically insignificant and transient, usually ceasing early during treatment. The few studies of ephedra herb in comparable dosage--and these are published studies--have failed to show any side effects whatsoever.

Now, why do we have this inconsistency? I believe that the FDA list has been compromised by the placebo effect. In the 1970s, I was with Organon, a pharmaceutical company in Holland, and we checked this out. We found if we gave patients placebo, told them to expect side effects, they did--a 35 percent quotient of side effects. And sometimes we got higher incidence of side effects with placebo than with the active.

The publicity surrounding the concerns about ephedra herb amounts to advertising for side effects, and it is not surprising that many are reported. However, leaving that question of validity aside, the numbers pale into insignificance against the enormous number of users of this herb. My estimate is 5 to 8 million Americans each year for 10 to 12 weeks, but other people have four times that estimate. So if we're talking over the last three years, 900 or 1,000 adverse effects, and during that time 24 or maybe 48 million Americans have used the herb for significant periods of time, I don't consider it as a very big problem, particularly if there is some concern about validity of the side effect list.

There is also the question of benefit. Though no claims may be made for dietary supplements, the fact that many Americans use ephedra herb for weight loss, often

successfully and sometimes when all else has failed, relates to a massive savings in health care costs and major health benefits for the users.

To view this in the real world, about 2,000 people die each year from eating chicken that has not been cooked properly. At least 30,000 people a year are admitted to emergency rooms with Tylenol or acetaminophen poisoning. About 300 of these die and many of the survivors have permanent liver damage.

Nutmeg, on a weight-for-weight basis, is far more dangerous than ephedra herb, and I have Jim Jukes(?) to thank for that one.

Moving on to the combination with caffeine, evidence indicates that the combination of ephedrine with caffeine may actually reduce some or all of the unwanted ephedrine-type effects, in particular those resulting from alpha receptor activation. Standard reference works of pharmacology teach that the beta adrenergic actions of ephedrine include dilation of the coronary arteries as well as some inotropic effect, but that the mild blood pressure elevating effect is due to the alpha adrenergic action. In fact, the results obtained by Astrup with an ephedrine/caffeine combination confirm this fact on re-evaluation, and there's also a letter appended to this

document from Astrup confirming that.

DR. LARSEN: Can you come to a conclusion in the next minute?

DR. JONES: Well, a lot of the things about caffeine are in here. Basically, there is one point that I think the committee should be aware of, and that is the interaction effect. On all our labels, we specify that people should not take cough or cold remedies or products containing appetite suppressants.

I believe this is a very wise precaution because the public is not informed. They need to be informed that ephedra herb does contain ephedrine and should not be combined with other products that contain ephedrine, phenylpropanolamine, fentamine, or any of the rest.

There have been some reports in the literature--and, in fact, Jukes' book on botanical medicine also mentions this--that yohimbine, which is present in yohimbe, may be a mild monoamine oxidase inhibitor, and therefore it would be wise if this was not combined with ma huang or ephedra herb in the same product.

We believe that all the perceived concerns can be fully alleviated by labeling, compositional restrictions, adherence to good manufacturing practice by manufacturers, and elimination of some marketing approaches. And we

believe that the FDA should be empowered to enforce anything which results in this action.

Finally, if the above is not sufficient, one extra line on the label will certainly kill the legal herbal street drug look-alike market: Warning--exceeding the maximum permitted intake may result in temporary impotence.

[Laughter.]

DR. JONES: Those who understand the roles of the catecholamines in mammalian physiology will appreciate the scientific rationale for this cautionary statement.

Thank you.

DR. LARSEN: Thank you. We have time for one question, if you have it, from the committee.

[No response.]

DR. LARSEN: Thank you, Dr. Jones.

Is Mr. Prochnow still in the room?

VOICE: No. He left.

DR. LARSEN: We'll put him on in the morning.

Dr. Dickinson, if you're still here, we'll let you go ahead at this point in time. Dr. Dickinson is Director of Scientific and Regulatory Affairs, Council for Responsible Nutrition here in Washington, D.C. While she's coming to the microphone, just before we started this open public hearing session, you were given a copy of the two

letters that I received from Mr. Gonzalez, Mr. Valori, and Mr. Nanney. I am told that Wendy Como is not going to be coming. I don't know at this point whether we will be getting a fax letter from her. And you do have in your packets a letter from Gail Harris, Director of the Texas Medical Association. In that letter, she indicates the resolutions from the Texas Medical Association which delineate facts they considered in their findings of its medical panel regarding products containing ephedrine alkaloids. Their conclusion, in essence, is that the product should only be available by prescription and under the supervision of a duly licensed physician. So that takes care of the letters that we've received so far.

Dr. Dickinson?

DR. DICKINSON: Thank you very much. I am Annette Dickinson. I'm Director of Scientific and Regulatory Affairs for the Council for Responsible Nutrition, which is a trade association of nutritional supplement manufacturers.

CRN joined with three other associations in supporting the joint position statement which was read to you this morning by Michael McGuffin of the American Herbal Products Association. We are looking to this committee and to FDA for guidance as to how to best deal with this issue that is before you today.

I have just three brief points that I would like to make in addition to the points made in our joint position statement.

The National Nutritional Foods Association brought to you this morning a medical witness, Dr. Michael Davidson, whom we all supported and whose testimony we have found very useful. We asked a medical expert to review the cases that are on the public record, because FDA had repeatedly said to us that we needed a better understanding of what those cases were.

Our intent in having him analyze those cases was--and I think he accomplished this--gaining a better understanding of the cases and trying to tease apart some of the differences between possible association with ephedra-containing products and those cases where there was more clearly a potentially causal relationship.

I bring up his statement only in order to make a quite different point. In the discussion that went on earlier this afternoon, there was reference to a couple of other statements that are currently being circulated and that will be presented at tomorrow's session from other industry associations or other companies, which in my opinion seem to be attempting to minimize or trivialize the reports that have been received here. I want to make it

clear on behalf of CRN, and I believe on behalf of these other associations that we have worked with, that we do not share in that intent and that, in fact, we deplore any effort to minimize the importance of these reports. We are taking them very seriously, and we are prepared to work with you in a serious manner to resolve them.

A second issue that I would like to address that was not addressed in our position paper has to do with good manufacturing practices. Dietary supplements are currently regulated under food good manufacturing practices. The Dietary Supplement Health and Education Act specifically authorizes FDA to adopt unique GMPs applicable to dietary supplements.

Soon after passage of the act, FDA officials contacted CRN and other industry organizations and asked for our help in developing appropriate GMPs for these products. I'm pleased to say that CRN, through its industry working group on quality standards, worked throughout 1995 and also the other associations were involved with us actively on this effort. And in November of 1995, we did submit to FDA a draft GMP document.

We have recently been notified by FDA that they consider that document to be very substantial and very helpful and definitely in the right direction and that FDA

intends to publish that document as an advance notice of public rulemaking for public comment. We're very pleased with this step forward and are anxious to see publication and eventually finalization of that document.

Thirdly, throughout this two or more years that we have been trying to deal with this ephedra issue, I think it has become increasingly clear both to the industry and to FDA that there are some real problems in the adverse reaction reporting system as we currently have to deal with it. Industry needs more information, needs to be able to come forward with more information on the denominators, as has been mentioned by several speakers here today. We need to be able to provide more conclusive information on the product content when cases are reported. FDA itself needs to be able to obtain quicker information about adverse reports that come to its field offices, and it needs to be able to more quickly notify the industry of those reports so that the industry can more promptly be involved in trying to resolve them so that we never again have a situation where we're faced, after the fact, with such a large number of adverse reactions.

Thank you very much.

DR. LARSEN: Thank you, Dr. Dickinson.

We have time for one question.

[No response.]

DR. LARSEN: No questions. Thank you.

One quick announcement. I realize that at some point during the afternoon we did not recognize the gentleman at the end of the table who is now conversing with Dr. Yetley. He is probably going to be embarrassed, but at any rate, Mr. Bill Schultz, Deputy Commissioner for Policy, is the person who was mysteriously missed when we did the introductions.

At this time, except for Mr. Prochnow who has agreed to go tomorrow morning, and the other folks who have asked to go tomorrow morning and those I have assigned tomorrow morning, this concludes this afternoon's scheduled open public hearing. I'll give one quick opportunity for anybody from the floor, if there are one or two people from the floor, I'll give you an opportunity at this time to make a brief statement to the committee.

I think it has been a long day and everybody's tired. I'm going to turn it back over to the Chairman to close the meeting down.

DR. ASKEW: I'd like to ask the committee members tonight, before tomorrow, to just kind of review the charge that's been given to us, the Food Advisory Committee, and kind of consider how you might individually answer these

questions that are presented to us. And this may form the basis of our discussion later on tomorrow afternoon.

We'll reconvene at 8:15 tomorrow morning. Thank you. It's been a long day. Thank you for your participation.

[Whereupon, at 5:17 p.m., the meeting was adjourned, to reconvene at 8:15 a.m., August 28, 1996.]