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P A R T I C I P A N T S

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Guest Speakers

James Prochnow, Attorney
Betsy Woodward, President, AFDO
Michael Betz, Attorney
Adam Gissen, Product Formulator
Steven Shaprio, Attorney
Gordon Peterson, Eola Products, Inc.

Calvin McClausland, M.D.
Blaine Wilson, Consumer

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

FDA

Dr. Lynn Larsen
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
Dr. David Kessler
Dr. Weintraub
Mr. William Schultz
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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 second day of our deliberations of the Food Advisory Committee concerning the potential health and safety problems that are associated with dietary supplements and food products containing botanical ingredients that are sources of ephedrine alkaloids.

Now, my name is Wayne Askew and I am chairing the meeting for Dr. Brandt who is recovering from an illness and his physician said that he should not travel. We introduced the committee yesterday around the table, so, I don't think we will go around and reintroduce everybody again. But I would like to note that we've been joined today by Dr. Susan Harlander, who is not at the table but she will be with us soon up here, to my immediate left and we're glad to have her here today. I believe that everybody else is pretty much the same.

Yesterday, we reviewed the subcommittee's recommendation, the subcommittee or working group on ephedra met in October of 1995, and prepared a report. We reviewed that report. We clarified the report and then stated that the purpose of this meeting was to consider the matter in greater detail in front of the entire committee.

We then had an open public hearing. We had

presentations on experience with the ephedrine-containing alkaloid in food products in Texas, Ohio and Canada. This committee was given a charge of what they were to consider and be ready to give their best opinion on with regard to safety issues today. And then we had a report on safety evaluation, second market review and another session of open public hearing at the end.

Today, we're going to start with a continuation of that open public hearing. We have a number of people who wish to address, in their seven-and-a-half-minute time period, the committee and then we were going to go into having a wrap-up and refocus and Dr. Yetley will bring us all back in to focus on the specific questions that the FDA wishes the committee to focus on.

Following that, we will have what everybody's kind of been waiting for, a chance to have open discussion. A lot of this discussion we have had to cut off because we have been having to move on to different points in the agenda. There will be plenty of time for open discussion.

Following the open discussion, we're going to go around the table and ask everybody to respond to the specific points that the FDA has asked us to respond to. We're going to respond individually and record the individual responses and a synthesis of that will basically

constitute our collective response to the FDA.

Then, finally at the very end, we're going to go around and I'm going to ask each and every person on the committee, voting member of the committee, if they endorse or accept the minutes of the working group, the previous working group that was held in October of 1995. And then give everybody a chance to make a statement, a wrap-up statement of their own, particularly with regard to their opinion as to the safety of this compound and any other issues that they have not had an opportunity to address.

So, you have a chance to get some very specific information, some general discussion and, finally, your view of the whole situation at the end.

We are ready now to move into the open public hearing. I will turn the microphone to the Executive Secretary of the Committee on Food Safety, Dr. Lynn Larsen.

DR. LARSEN: Thank you.

One quick announcement. I noticed some folks passing materials out to committee members. I would appreciate it if you would check with the staff so that you could make sure that each committee member got materials and including a copy at least for the record of the meeting.

Someone was asking me earlier about the difference between the wire-bound copies from the Ad Hoc Committee on

Ma Huang and the bound copy that we got yesterday. Some people seem to have wire-bound and plastic bound. I don't know what the difference between those is. And I notice that not everybody has the wire-bound one. So, if whoever passed those out would talk to the staff and make sure everybody on the committee has a complete set and that is everybody has a set, as well as for the record.

VOICE: Lynn, they're identical except for the binding.

DR. LARSEN: Thank you.

I thought from the front they looked like they were identical except for the bindings. So, those that have two copies don't really need two copies.

We've got quite a number of folks that, because of the changes in the schedule yesterday, who are in the open public hearing this morning, so we want to try to move along as quickly as possible. We may not get a chance to have as many questions as we ended up allowing yesterday. So, if the committee, as you listen to these and if you have a question, try and make it succinct so the answer can also be succinct.

The first speaker this morning then is Mr. James Prochnow, an attorney from Patton Boggs in Denver, Colorado. And, as yesterday, if each of you would re-announce your

name, your affiliation, and so forth, so that it is clear for the record, and you have seven-and-a-half minutes.

MR. PROCHNOW: Thank you.

My name is Jim Prochnow. That is P-R-O--C-H-N-O-W. I'm a partner in the Denver office of the Washington, D.C. based law firm of Patton Boggs. I'm excited to speak to you today for three reasons: one, I'm expected to become a grandfather for the first time today so I need to get back to Denver as soon as possible; second of all, I had a great jog between the Washington Monument and the Capitol last night; thirdly, the subject matter of today's presentation.

When I was a young man, as defined yesterday by somebody in this group, I was a trial lawyer at the Department of Justice here in Washington. I want to let you know I respect the task which you and the FDA has and which you're confronting today.

I specialize in the representation of dietary supplements manufacturers, distributors and retailers, most are relatively small businesses, who are ordinary people; people who are very concerned about the safety of the products which they sell, since, among other things, their spouses, friends and neighbors consume them.

For the most part, these people have been manufacturing, distributing dietary supplements which

contain ephedrine alkaloids for a decade without any serious adverse reactions being reported to them and these are people who are not blind to adverse reaction reports.

Now, some of the products that are represented by these people yesterday were over on the table that the FDA had. I want to say that the companies which I represent are also members of the American Herbal Products Association and the NNFA, both of whom you heard from yesterday.

Today I speak and have three major recommendations and three principle points which I wish to make. They are the following:

First of all, I speak in firm support for the position taken by the NNFA yesterday and the American Herbal Products Association. Now, those two groups represent a variety of dietary supplement companies and not just those companies that manufacture products that contain the ephedrine alkaloids.

Second of all, the second recommendation that I wish to make is I believe that the proposed regulation which addresses dosage or, in food language, serving size should be issued as a "safe harbor provision" pursuant to new section 402(f)(1)(d) of the Federal Food, Drug and Cosmetic Act, sometimes known as the deleterious substance provision. I know that's a technical matter but it's something that I

want to leave with you.

And, thirdly, I propose that the Office of Dietary Supplements within the National Institutes of Health or the FDA joint venture a reliable clinical study on the acute and long-term safety of ephedrine alkaloid dietary supplement products.

As the committee continues its work I strongly urge you to keep in mind that over-regulation is more pernicious to the American public than under-regulation. Vice President Gore's national performance review and the reinventing of government initiative are reminders of this principle.

The other major global point I now make is that the law of this land and the law under which you must proceed and must understand is the Dietary Supplement, Health and Education Act of 1994. Frankly, it's revolutionary. It's effective throughout the United States, including Texas and Ohio.

If some States or government-related bodies ignore this law, DSHEA must be amended to preempt State laws which purport to deal with dietary supplements. Now, I've enclosed, as a part of my presentation today, an up-to-date as of yesterday survey of all 50 States and how they govern ephedrine-containing dietary supplements. There are only a

couple of them which clearly, at the present time, ban dietary supplements with ephedra and basically those are Ohio and Nebraska.

There's kind of a matrix that's in some cases very ambiguous of how State laws govern dietary supplements because many of them define ephedrine as a precursor of controlled substances. So, we have a very elaborate table to leave for your consideration.

DSHEA reflects special laws for dietary supplements which are not applicable to conventional food and drug products. This must be understood. Three of those unique provisions are the creation of a special legal category of goods called dietary supplements. For example, there's no requirement that nutritive value be present. And, in my opinion, a dietary supplement, as legal counsel for the FDA pointed out, can be non-natural in nature; whether an ingredient is natural or not is a mis-branding issue, not a safety issue.

Secondly, there are special safety laws that this committee must consider. And, thirdly, there's the infamous structure/function provision.

One word about this last new law. That is basically that a dietary supplement manufacture is able to inform each consumer of how a supplement or one of its

ingredients affects the function and structure of the human body as long as it is not promoted to prevent, diagnose, mitigate or treat or cure a disease.

As a result, a statement that a particular dietary supplement is effective for weight loss, mental alertness or clarity or for just plain energy does not make that related product a drug as defined by the Federal Food, Drug and Cosmetic Act. As you can tell, the law in Canada is significantly different.

Of these, the adulteration or safety provisions of the Dietary Supplement Health and Education Act are the most critical. It is appropriately entitled the Safety of Dietary Supplements and Burden of Proof on the FDA. Section 402 of the Federal Food, Drug and Cosmetic Act was amended by DSHEA by adding a new sup-part (f)(1) to (20. There, the Congress explicitly stated that a dietary supplement will be deemed to be adulterated only if one or more of four tests are proven by the FDA. This is the Congress talking, this is not me.

The three main ones are this: A dietary supplement is only unsafe or adulterated if it presents a significant or unreasonable risk under conditions of use suggested in the label.

Secondly, if the Secretary of HHS, not the FDA,

declares that ingredient--since it's an ephedrine alkaloid--to be an imminent hazard to the public health or safety. And, thirdly, whether it is poisonous or deleterious.

In this case, I think a safe harbor provision is the way to address this issue because of other specific provisions in the Act which talk about the fact that a manufacture does not have to disclose all the quantity of ingredients in a proprietary blend.

Now, because my time is running out, let me say something else about the safety of ephedrine-containing dietary supplements. There are about 60 cases in Texas right now that we are defending involving Formula One. Some have been dismissed by the plaintiffs, some have settled and some are going to be tried just like a normal lawsuit situation. But the crucible of litigation is revealing a lot of important facts because it is only there, where the full medical records of people are disclosed, when Formula One and other dietary supplements were ingested and related to the purported causes for things. Guilt by association is not enough in a court of law and should be not enough for this committee.

Lastly, what I want to say is this: I'm proposing--during the course of the last six months a major dietary supplement manufacturer proposed a protocol for a

long-term and acute study of dietary supplements to be done at Harvard and Vanderbilt University with respect to ephedrine-containing alkaloids.

Because of the cost involved it was not actually done but the protocol was approved by Harvard and Vanderbilt Universities to be conducted by Dr. Patricia Daley who really is the only one who has done substantial studies in this issue. The FDA was initially consulted generally about this.

I propose that in addition to the good work that this committee does today that the FDA or the Office of Special Nutritionals, as authorized by Section 13 of the Dietary Supplement Health and Education Act, consider carrying through with those studies. A tremendous amount of dollars and energy has already been expended on developing that protocol and it would be consistent with the spirit and language of the Dietary Supplement Health and Education Act for that type of study to be finished.

In closing, let me summarize by saying this: I think that the proposal of the American Herbal Products Association and the NNFA is a solid proposal which is the consensus of almost every company in this industry. We have some who believe that no conciliatory effort is necessary. We have others who feel that the proposal is too far

reaching. But, in my judgment, based upon the thousands of issues that I deal with each week in the area of dietary supplements, it's a good proposal and a good way for this committee to meet its burden of assuring safety to dietary supplements and not over-regulating.

Thank you very much for your attention to these remarks. I think I will go over and have a cup of coffee.

Thank you.

DR. LARSEN: Thank you.

Time for one question from the committee.

Dr. Applebaum?

DR. APPLEBAUM: Yes. I have a question concerning the proposal for the clinical study and your mentioning of Dr. Daley being one of the experts in this issue. Do you have any information on her view as for the safe level of dietary supplements?

MR. PROCHNOW: Well, let me put it like this. The Institutional Review Boards of Harvard and Vanderbilt on a preliminary test they go through would not probably have approved the protocol for these studies unless they felt that there was a good possibility or probability that the levels of ephedrine that were going to be tested, about 25 milligrams per dosage or serving size in terms of food, was an appropriate safe level.

Now, I don't want to say that Dr. Daley would prejudge the results in advance, but the parameters of the protocol included at least 30 milligrams of caffeine per serving size and at least 25 milligrams of ephedrine alkaloids per serving size.

DR. APPLEBAUM: Correct. But they're probably looking at a finite time frame for this study? And they're very critical in the selection of their subjects.

MR. PROCHNOW: No. This was a six-month rigorous protocol developed. But I will be happy to make it available to this committee. It was a double-blind cross-over, you know, a placebo group as well as an active group of participants of at least 300 people.

DR. APPLEBAUM: Okay. And then my final question is, what has prompted the industry to pursue the proposal?

MR. PROCHNOW: Well--

DR. APPLEBAUM: I mean what made them decide to even initiate the study in the first place?

MR. PROCHNOW: The answer specifically is this: This industry, over the last four years, is a changed industry. People are doing things they never did before. Not only because of the pressure in the government, because of the pressure of competition, given by the Dietary Supplement Health and Education Act.

So, one of the things that's going on every day now are substantiation studies and clinical studies for dietary supplements. One of the company's felt that this would be a good way to deal with issues that had arisen.

DR. APPLEBAUM: Thank you.

DR. LARSEN: Thank you.

We can now move on to the next speaker.

MR. PROCHNOW: Thanks for your attention.

DR. LARSEN: The next speaker is Ms. Betsy Woodward, President of the Association of Food and Drug Officials. Her employer is the Department of Agriculture in Florida.

And if you can repeat your name for the record and make sure that what I've said about your employment and affiliation is correct.

You have seven-and-a-half-minutes.

MS. WOODWARD: Thank you, Dr. Larsen.

My name is Betsy Woodward, and I am President of the Association of Food and Drug Officials and I'm employed by the Florida Department of Agriculture and Consumer Services.

The Association of Food and Drug Officials is a 100-year old organization representing Federal, State, and local food, drug, device and consumer product safety

officials, along with academia and industry associates through its national membership and the membership of its six regional affiliates.

Therefore, AFDO is a major voice in addressing food, drug, device and consumer product safety issues. Our primary focus is the basic constitutional role of government, consumer protection, by ensuring that products are safe and properly represented in their labeling.

For the past two years, both at the 1995 and 1996 annual education conferences, AFDO has addressed the issue of dietary supplements and, in particular, ephedrine products. In 1995, the AFDO membership voted unanimously to support a resolution recommending the "removal of ephedrine products both natural and synthetic from over-the-counter sales status as a food dietary supplement and a drug."

And I'm attaching these resolutions to the testimony.

In 1996, the Association unanimously voted to support a resolution which opposes the marketing of potentially dangerous herbal compounds as legal substitutes for elicit drugs, such as the use of Ma Huang as a substitute for speed.

These resolutions reflect a growing concern by the State officials at both conferences of the continuing

proliferation of reports of adverse reactions and deaths associated with ephedrine consumption, not only from product abuse but also by product use.

Florida officials have reported on a death attributable only to the consumption of a ma huang caffeine product. Analysis of more than 60 ephedrine products, represented as dietary supplements, by the Florida officials have shown some products with ephedrine alkaloids up to 100 or better milligrams per dose.

One product label offers 190 milligrams per dose. Fortunately it did not meet its label claim when analyzed by Florida scientists.

School nurses in Florida reported numerous adverse reactions among their high school students, such as heart arrhythmias, nervousness, sweating and insomnia. Several students have been referred to emergency rooms. These incidents have gone largely unreported since the School Nurse Association was totally unaware of the Med-Alert reporting system.

In June of 1996, AFDO testified before the Commission on Dietary Supplement Labels. In that testimony AFDO stated safety cannot be separated from label information and has life and health implications with these products. The States continue to struggle with the

proliferation of both health and labeling issues related to ephedrine products and the fact that these products represent the most abused herbal supplement.

After hundreds of reports of adverse reaction, 15 deaths--including the one in Florida--and much discussion at the annual conferences, it is clearly our opinion that these products should be regulated as drugs. The adverse reactions are generally consistent with the pharmacological effects and adverse reaction of ephedrine alkaloids, synthetic or natural, documented in the medical literature and published reports.

It is clear from the death in Panama City that the reactions resulting from ephedrine consumption can be unpredictable. Three young men consumed the same dose. Two survived and one died. The young man who died had a blood alcohol level of zero and no other compounds were found in his body and no other abnormalities were noted on autopsy.

AFDO is also concerned with the marketing and labeling of foods containing ephedrine alkaloids as all natural or all herbal--implying natural is not only safe, it is better. Poison and hemlock are natural but they certainly are not safe.

There is an inconsistency in a public health policy which requires food additives to be approved as safe,

yet, ephedrine herbal supplements have no approval process and the consumer is not knowledgeable to the extent necessary to safely consume ephedrine products.

The use of botanical names in product ingredient statements is a major concern. Again, the average consumer is totally unaware of what the term means and certainly has no idea as to the pharmacologically active ingredient in that particular botanical, nor an understanding of the adverse reactions, contraindications, or other drug product interactions which affect safety.

When consumers lack the scientific knowledge to make a judgment so critical to safety, efficacy or appropriateness of a product for consumption by that consumer, government has a constitutional and moral responsibility to provide controls to ensure safety.

Of greater concern is the combination of ephedrine with other stimulants and/or the lack of warning not to consume other stimulants. The threat of adverse reactions increases with the synergistic effect of other stimulants such as caffeine causing an over-stimulation of the central nervous system.

While the intent of the Dietary Supplement Health and Education Act of 1994 was to educate the consumer about a more healthy lifestyle the actual result, with respect,

particularly to the ephedrine alkaloid products, has been the hundreds of adverse reactions, the misuse, abuse and even deaths being reported. On September 22nd, 1995, AFDO recommended that the FDA classify all ephedrine-containing products as prescription drugs.

Florida has taken the role that ephedrine alkaloid products exceeding the current OTC monograph levels are adulterated foods. And that failure to provide information on the presence and the amount of ephedrine alkaloids, along with information regarding adverse reactions, contraindications, other drug interactions and clear directions for use constitutes failure to provide material information relating to the product's safe use. A majority of States have regulations dealing with ephedrine to some degree.

Clearly, clearly, the States are speaking to the issue with one voice and that voice says that government has a duty to protect the public health and safety here. We believe that the FDA should, at best, prohibit the use of ephedrine alkaloids as food, food additives or dietary supplements and, at worst, strictly control the ephedrine levels and the sale, while mandating a system of tracking adverse reactions.

AFDO's model is uniformity through communication

and cooperation. We are prepared to work with the FDA in protecting the public health and safety; as food and drug officials we all have a constitutional and statutory duty to do so.

I thank you for the opportunity to present these remarks.

DR. LARSEN: Thank you.

We have one question. Dr. Ziment?

DR. ZIMENT: I'm impressed by the comment that ephedrine and other stimulants, acting together, maybe synergistic to the disadvantage to the patient. Are you aware of whether standard textbooks or guidelines to drug usage make this point so that doctors, in general, are aware that caffeine added to ephedrine as a prescribed drug or recommended drug could be dangerous?

Because I'm not aware of that.

MS. WOODWARD: I'm not aware of that either. But then I'm not a doctor so I wouldn't necessarily see those particular journals.

DR. ZIMENT: I'm not talking about journals. I'm talking about standard textbooks, including the Physician's Desk Reference.

MS. WOODWARD: Okay.

DR. LARSEN: Thank you.

We want to move on now to the next speaker. The next speaker is Mr. Michael Betz, of Banowsky, Betz and Levine, representing Omnutrition International, Incorporated.

And as I keep saying, please repeat your name and your affiliation so that we have it clear for the record and you have seven-and-a-half-minutes.

MR. BETZ: Thank you, Dr. Larsen.

Mr. Chairman, and members of the committee, thank you.

My name is Mike Betz, and I'm with the Dallas law firm of Banowsky, Betz and Levine. We represent Omnutrition International, a distributor of dietary supplements.

As with every responsible manufacturer and distributor of dietary supplements, Omnutrition is concerned about this report and the adverse effects reported in the report. At the same time, I'm disappointed to say that we're also concerned about the accuracy of this report.

I came before the working group 10 months ago and the members of the working group will remember that I was here and I pointed out at that time several instances in this report of Omnutrition's products, contained within the report, which contained no ephedrine alkaloids.

And I watched as everybody dutifully wrote this

down, and 10 months later, they're still in this report. And our concern is that this is more about compiling big numbers than accuracy. The charge of this committee was to do science, to take a scientific approach to this problem, to the extent that it exists.

And I contend it's very difficult to do that if you're not going to have accurate information provided to you. And I want to go through some of these. Since I did it last time, I only had five minutes and I've got seven this time. I will try to go through them pretty quickly. But I want to go through the particular ARMS reports for the committee.

If you look at page three of your report, ARMs-8904, you'll see this person had chest pains and difficulty breathing and body tremors. They took a product which is listed here as WOW--I believe it is Wide Awake is the name of the product; it's not a product that Omnutrition carries any more, but it was simply a caffeine-based vitamin drink which had a little less caffeine than a cup of coffee--Focus, which is a choline supplement, and Fiber N'More which is a fiber product much like Citrucel, Metamucil or one of those products.

DR. LARSEN: Do you have a page number to help the committee?

MR. BETZ: Yes. The page number is page three on the report.

DR. LARSEN: Thank you.

MR. BETZ: And again, it's 8904. And, although, I pointed out last time that these three products contain absolutely no ephedrine alkaloids, they're still in the report as part of this larger report. And I might add, a quarter of the times that Omnutrition's products appear in here, they contain no ephedrine alkaloids.

The next one is on page five. If you look at ARMS-9144, it now says, products, Omnutrition's vitamins and food supplements. If you read the little narrative it says the person took WOW again--that's a caffeine product--Omni IV, which is a multi-vitamin, and Focus, which is a choline supplement. And, again, this person's having some kind of hyper manic depression and hyper-mental status changes and insomnia.

The amount of caffeine, which as far as I can tell, is the only one of these three products that could have any pharmacological effects, that would cause that is less than that contained in a cup of coffee.

If you go to page 14, and you look at ARMS-9483, this person again took WOW or Wide Awake, which is a caffeine product. Again, no ephedrine alkaloids whatsoever.

If you go to page 57 of your report and you look at ARMS-10248, you'll see the person took WOW again, a caffeine drink, and Focus, which is a choline supplement. Again, no ephedrine alkaloids whatsoever.

And it goes on. I can tell you the other ones are on page 58, and they are ARMS-10249 and 10250. And, again, I point this out for the second time because as I said, we were very disappointed when we came back to see that these were still here.

We want to be part of the solution. We want to work with the FDA and the NNFA and the other groups, the Ad Hoc Committee to approach this problem responsibility but to do that you need to have accurate information. And it's just, in light of the fact that I was here and pointed them out specifically by number last time, it's unconscionable that they're still part of this report if what this committee is trying to do is establish science.

A second point I want to make is that Dr. Jasinski, yesterday, asked about the numerator and denominator and said, well, we don't have a denominator. I want to try to put that in perspective.

Over the past five years, Omnutrition has sold approximately 100 million servings of ephedra-based products. We believe that our position in the market is

relatively small, probably around 5 percent of the market share. If you assume it's 10 percent, if you move out on a limb and assume it's 10 percent, that's over the last five years, one billion servings of ephedra-based products.

And I think that puts us in a perspective. I mean last time, before the working group, I noted that--I believe it was--Dr. Jasinski again mentioned at that time that we don't know whether we are dealing with a large numbers problem when we see this number of reports.

And, to the extent that you're looking at one billion servings over five years that may, in fact, be what's taking place here.

We would urge that the committee adopt the working group's recommendations. We believe that the working group considered this matter thoughtfully and we believe that it's a responsible approach.

Omnutrition's products have conformed to those recommendations and have done so for years prior to the time of the working group's recommendations. And with one hundred million servings our experience is dramatically different than what would be suggested by this report.

We are aware of a few side effects, minor side effects by a very small number of people. We are not aware of the types of reports that make up the bulk of the

clinical summaries and adverse event reports that are before the committee.

Accordingly, we believe that the reason for that is that we have complied with the working group's recommendations. We believe that the labeling that we have which has a strong cautionary statement allows the consumer to read the cautionary statement and to not take--and I see the light's blinking--not take the product where it's not indicated, not take the product in combination with certain other conditions or drugs where it might be contraindicated.

And with that, since I appear to be out of time, I'll thank the committee for their time and again urge the committee to adopt and accept the working group's recommendations as a reasonable measure to ensure the safety and health of the American citizens.

DR. LARSEN: Thank you.

We have time for one question. And I would ask that this question be addressed to the speaker. I can see where there might be questions addressed to other folks from this presentation, but I think we want to hold that until your committee discussions. So, if you have a question for the speaker, himself.

Dr. Ziment?

DR. ZIMENT: Although you say one billion servings

have been sold over five years, that means 200 million a year and I would guess that the average consumer takes what, 50 to 100 servings, which may mean one or two million people are taking this drug. Now, the real question for me is what percentage of one million people who take a drug should be allowed to have adverse reactions before control is taken?

MR. BETZ: I would just say that I can't--I'm not a doctor--I can't speak to that issue. I would say, though, that our estimates, our understanding of the estimates with respect to the number of people in the United States who are actually using ephedra-based dietary supplements is higher than one to two million people. It is more on the order of perhaps 10 to 20 million people, who have used at some point in the last five years ephedra-based supplements.

DR. ZIMENT: Well, if they do use it, what are they using it for?

MR. BETZ: Some people use it--

DR. ZIMENT: Because just--I wouldn't think anybody could use a dietary supplement in one or two doses and get any benefit. If you're going to get benefit, you would have to take it for what, a month, two months?

MR. BETZ: People use the product for different reasons. Some people use it for bronchial--

DR. ZIMENT: Not many.

MR. BETZ: Some people use the products--

DR. ZIMENT: No, I'm talking about the dietary supplements.

MR. BETZ: Right. And some people there use the product for its stimulant effect much like people would take a cup of coffee. Other people use the product--

DR. ZIMENT: Oh, people take a cup of coffee every day. So, what I'm wondering about is really how many people take it on a regular basis and how many of those people are getting into trouble?

MR. BETZ: All I can say is the numbers that we have looked at indicate that the market is between 10 and 20 million Americans that have used the product overt the last five years. And I can't, unfortunately I can't answer--I don't have the data to answer that question. I don't think I would contribute anything to the science.

DR. LARSEN: We have two other questions.

Are they of this speaker? Okay.

Ms. Richardson?

MS. RICHARDSON: You just mentioned 10 or 20 million people have used it over a period of time, but the question is, is, I mean if the product is working and is so beneficial then why is there such a large turnover? I mean are these people, in fact, do they, in fact, stop using the

product because they have these, as you call them, minor side effects, which they may not seek medical help for or report to MedWatch?

MR. BETZ: That's not been our experience with the product.

DR. LARSEN: Dr. Harlander?

DR. HARLANDER: Can you tell me if you have a 1-800 number on your products where people who have adverse reactions can call into the company and report those to you? Or, how do you track adverse reactions to your products? How do people get in touch with you and let you know that they've had a problem?

MR. BETZ: With our products, all of the products, if people are dissatisfied with the product there is an 800-number. I'm not certain if it's on the product or it's on other materials that they have regarding what's in the products and the catalog, for example. But the way that we get information about the products is people who take the products who are dissatisfied with the product, for whatever reason, will report to the company and often seek a refund for the product. And at that time, some people will say they had this problem or that problem, they will say they didn't like the taste.

Most of the returns we get are people who say they

didn't like the taste or thought they didn't lose weight on the product or whatever other thing or benefit they thought they were going to get from the product. The vast majority of them are not related to the types of reports that are seen in the advisory committee's clinical summaries or the clinical summaries, I'm sorry, presented to the advisory committee.

And those that we have seen, as I said, are minor in nature, people who report that they feel jittery or nervous from the product and will return it on that basis.

DR. HARLANDER: But you do track those and keep those?

MR. BETZ: Yes, we do.

DR. LARSEN: Thank you, Mr. Betz.

The next speaker is Mr. Adam Gissen and I only have him listed as a product formulator. So, if you would please make clear for the record your affiliation, I would appreciate it.

Thank you.

MR. GISSEN: Good morning.

My name is Adam Gissen. I am a product formulator. I'm also a bio-chemist. I'm here representing Omnutrition International and I have been involved personally in the development of approximately half a dozen

different products that contain ephedra alkaloids as one of their ingredients.

And I also testified here approximately 10 months ago, as the previous speaker, and raised the question that I'm also surprised has not been further addressed to any extent at all.

That is simply that up until now ephedra-containing products have been regulated as foods just as other dietary supplements have. And what was quite surprising to me initially was looking at the types of side effects that have been reported many of them do not fit the typical side effect profile that you would expect from ephedrine. And, of course, ephedrine has been sold in this country over-the-counter for many, many decades without this same kind of almost hysterical incidents of strange side effects that have occurred with products that are used rather as food that contain ephedra alkaloids.

And what I would think, first of all, as a scientist looking at that, is that when you have some side effects that are unrelated to what you would expect from somebody that even took an overdose of ephedra--and remember there's a long history of use of ephedrine-containing products, including a long history of people trying to use those products to kill themselves--and usually other than

supportive measures most people taking even pretty astronomical amounts of ephedrine alkaloids usually recover completely, as opposed to some of the stranger side effects, many of them occurring from just one dose and causing permanent harm.

And the issue I raised last time that I don't think has been addressed at all is that if we are dealing with people being harmed by a food product why hasn't the potential cause of the harm been investigated as it would be with other food products? What I'm talking about is the presence of other things such as contaminants, both naturally occurring microbial contaminants, as well as man-made contaminants.

Now, we have to remember that we are dealing with an herbal product. And most of this product is produced in other countries, namely the Far East. And it's my understanding that none of the product that has caused harm, including harm that would not necessarily be consistent with harm from ephedrine or ephedra alkaloids, that the possibility that instead there are other things contributing to this problem have not at all been addressed, despite the fact that it is a food product. And this has not only occurred on the Federal level, but also in individual States.

The other thing that I think is very important to look at when you look at these injuries is how many of these are preventable injuries? In other words, how many of these people ended up harmed because they did not follow reasonable caution when using these products?

Certainly we can't expect the people trying to kill themselves or people taking something like ephedra alkaloids with--when I was looking earlier I saw one particular case where the person was in a trial for Prozac. And although the person didn't know if he was in the placebo or the group that received Prozac while he was taking an ephedra product, they asked the study coordinator if he thought that Prozac could have any cause or any relation to this person's injuries and the report states, no.

And anybody that knows anything about the pharmacological profile of ephedra alkaloids would have to assume that it's certainly possible that a neurologically active chemical like Prozac could interact with ephedra or ephedra alkaloids. And I think that's an important thing to remember when looking at the possibility of contamination.

Certainly if there are things like unapproved pesticides that are in these products, one would have to assume that the neurologically active contaminants could synergistically react with ephedra alkaloids and result in

side effects or injuries or harm that would be completely inconsistent with what you'd expect from ephedra or that other contaminating agent.

In other words, that the combination would result in injuries that neither ingredient on its own would cause. This has certainly been demonstrated over and over scientifically with other chemicals or ingredients that are active on the central nervous system. And there's no reason to assume that the same could not be true with ephedra.

As far as the recommendations, one of the most telling things has been the desire to limit the use of products like this to some duration of time. This is in spite of a complete lack of scientific information indicating that this makes the product safer or more effective.

In fact, many of the studies, in fact, all of the studies that have been done on ephedra have been done over a duration significantly longer than one week. However, what you can be sure of is that by limiting the use to one week you completely negate what the scientific community has been so excited about in relation to ephedrine or ephedra alkaloids and that is that these products have negative tolerance when looking at their effect on the central nervous system.

And that's one of the things that makes something like ephedra a real poor alternative to speed. People develop tolerance very, very rapidly to the effects of ephedra on the central nervous system, especially used responsibly, in other words, starting at a low dose and slowly building up to some recommended level.

I can tell you that the people I've spoken to--and I've spoken to literally thousands of users that have used products both that I've developed and other people have developed--that the incidents of side effects when used properly, as I've just described, and when taken in light of the fact that certain warnings or cautions should apply to ephedra-containing products and products that I designed have extensive warnings, when used in light of those warnings and not taken when contra-indicated, and use responsibly over any period of time, the product is safe.

If you try to limit its use, people are certainly not going to take something that you want to build up to the full dose over 10 days to two weeks, that's not possible to do in one week. And if the incidents of problems with this product are due to some synergy between ephedra alkaloids and some other possible contaminants in the products, that would certainly do nothing at all to prevent possible harm to the public.

I think that, you know, a good example of this and something that I was thinking about is nicotine gum. Certainly gum is considered food and nicotine gum is now allowed to be sold over-the-counter in this country. This is in spite of the fact that nicotine is now a recognized addictive drug, that's officially recognized. It has been scientifically recognized for decades.

Certainly if people can responsibly use an addictive drug that is now a scheduled drug then certainly all of these people that have been put together should have the intelligence to come up with recommendations that enhance the public's safe use of these products without unnecessarily restricting their use.

And if our main interest is to protect people from harm and certainly the biggest problem now with ephedra containing products--

DR. LARSEN: Can you please wrap it up?

MR. GISSEN: Yes--are the potential for abuse. Taking this product off the market is going to do nothing but increase people's interest in obtaining it illegally and product that is possibly even more dangerous than available now, and certainly in the case of children--I will wrap up in 10 seconds--but one of the things I heard is that since all the attention on these, you know, herbal ephedra

products that are supposed to be used as alternatives to hallucinogens, that the actual usage of those products and interest has increased dramatically.

By applying science to this problem we can help people and we can prevent them from harming themselves. But we run the risk when being unscientific and reactionary of actually increasing the potential for problematic use of ephedra herb.

Thank you.

DR. LARSEN: Thank you.

Oh, we got a whole bunch of questions.

We will start with Dr. Fong. Make sure you address your questions to the speaker.

DR. FONG: You spoke with allusion to the fact that perhaps some adverse events may be associated not with the product but from the source of the material from the Far East by contamination of pesticides and so on and so forth and all that stuff. Assuming that you are correct, I am, as a pharmacist, I am very, very offended that industry, the manufacturer do not take responsibility to have quality control. That you do not do GMP, or quality assurance. Certainly you can detect pesticides and any other contaminant.

So, excuse me for being emotional but I do find

that offensive to pass the blame onto somebody else.

MR. GISSEN: Well, there's no insult intended, if I can respond. However, I am personally responsible for sourcing materials for the products I develop. And we have to remember that these are food products and herbs are food products.

And like anybody else that is involved with designing foods--and this would apply to people that are making processed American cheese as well as people selling ephedra herbal products--there are unscrupulous people in this world. And there's no way around that.

And certainly the companies that I represent and that I design products for strictly abide by GMP procedures. However, there is absolutely nothing in GMP procedures that states that any manufacturer is required--and this goes for foods, nutritionals across the board--are required to test any product for the residues of pesticide, herbicide, fungicides, microbial. I mean literally you are talking about something that would be so prohibitively expensive.

Instead, the responsibility is with the regulatory agencies. That when there is a potential problem with a food product, the way that they have traditionally found the source of the problem and removed it from the market place is to immediately assume that any health problem related to

a food product has at least the potential to be caused by contamination.

And that's what has been shocking to me, that this issue has not even been addressed.

DR. LARSEN: Mr. Ford?

MR. FORD: Mr. Gissen, I heard you make this assertion the last time you testified before the group. And your supposition is that it is contamination in these products that is the basis of a report containing 618 injuries and 30-some odd deaths? That it's just a case of contamination?

MR. GISSEN: Well, my supposition is that, you know, if you look at the report in its entirety, and certainly there are injuries that have occurred from people that are strictly related to ephedrine. The question is, are these people being harmed at reasonable usage?

And I think that a large number, if not the vast majority of these cases, are from people abusing the product. However, there is no reason to not assume that even at reasonable levels of ephedra alkaloids the possibility of some synergistic negative side effect that could be quite severe could be caused by the interaction of the ephedra alkaloids which affect the central nervous system with some other contaminant that may affect the

central nervous system.

MR. FORD: Does Omnutrition have ma huang products, though? I understand there are injuries listed in the report that are inaccurate, but do you have any ma huang products?

MR. GISSEN: When you say, do I have any, you mean the companies that I design products for?

MR. FORD: Well, you identified yourself with Omnutrition.

MR. GISSEN: I'm here today representing Omnutrition.

MR. FORD: Right. So, do you--

MR. GISSEN: They do have products containing ma huang.

MR. FORD: They do?

MR. GISSEN: Yes, they do.

MR. FORD: And do you participate at all in the inspection of the materials that are taken in to make the end products?

MR. GISSEN: The materials are both analyzed by the primary manufacturer and are--

MR. FORD: Do you participate at all?

MR. GISSEN: Personally?

MR. FORD: Yes.

MR. GISSEN: No. I'm a product formulator. I'm not an analytical chemist.

MR. FORD: Well, maybe you should. And please when you reference GMPs that have been put forward in a draft format to the FDA by the four cooperating organizations that deal with this issue and we certainly expect the members of our organizations to meet, if not exceed, those GMPs and we do expect that companies are well aware of their source material before anything is made into an end product.

MR. GISSEN: I, personally, have seen product that has actually been sent from primary manufacturers that took the time to do the right thing and analyze their products for microbial contamination that tested positive either for E. coli, or salmonella where I was actually sent a sample of product to look at with the prospect of purchasing it that was sent along with a certificate of analysis that basically said this product is contaminated.

MR. FORD: I don't think you're taking my point.

MR. GISSEN: Okay.

DR. LARSEN: Thank you.

Dr. Inchiosa?

DR. INCHIOSA: Thank you.

Mr. Gissen, you mentioned that there were effects

in the report or adverse reactions which were not consistent with the known pharmacology of ephedrine alkaloids. What are you alluding to there?

MR. GISSEN: Well, I'm going both on the reports contained here and also the ones I've seen from other States. You know, for instance, if you look at, you know, cases of people that have taken say ephedrine sulfate--and there are cases in the literature of people literally taking thousands of milligrams, usually with supportive measures, these people will completely recover.

MR. FORD: No. It was the other point you made. You said that there were adverse reactions that were not typical.

MR. GISSEN: I've seen things, not typical, that look like food poisoning. Things that looked like chemically induced hepatitis. Things that you would really not expect from ephedrine poisoning, but certainly could be caused by a combination of--

MR. FORD: Actually, you're incorrect there. The gastrointestinal effects of ephedrine are well understood. It has to do with constriction of the mesenteric bed. So, you do get hepatitis, increase in liver enzymes. You get all types of gastrointestinal upset.

MR. GISSEN: I'm balancing this against cases of

people taking, for instance, one dose or one serving of, say, 25 or 30 milligrams of ephedrine alkaloids and receiving permanent harm.

Now, certainly that would not be considered part of the pharmacological profile of ephedra alkaloids.

MR. FORD: But don't dismiss the gastrointestinal effects.

MR. GISSEN: Maybe that's a bad example.

MR. FORD: A very bad example.

MR. GISSEN: But there are certainly cases of people receiving harm from ephedra products that look, you know, if nothing else look somewhat strange. That they have aspects to them that are surprising.

I mean certainly you would have to say that it's surprising that someone could take tens of milligrams of ephedra alkaloids and be so severely harmed when we know that there are people who are routinely abusing it, as well as people trying to commit suicide, even with pure, you know, pharmaceutical grade ephedrine sulfate that are not receiving the same types of injury or the same types of permanent harm.

All I'm raising--I am not saying that this is definitive--but it certainly is a possibility, and if we are going to be scientific about it, it would certainly be a

shame to take the product off the market when the problem is actually one that we're not addressing.

MR. FORD: Yes. But from a scientific standpoint, the adverse reactions are consistent overwhelmingly with the known pharmacology of ephedrine.

MR. GISSEN: You're saying that for every case that's been found?

MR. FORD: I'm not saying every case. I was saying overwhelmingly.

MR. GISSEN: Oh, I would agree. There is certainly overwhelmingly people are not being harmed. I certainly would say the vast majority of people--

MR. FORD: I said they are overwhelmingly reported--

DR. LARSEN: Excuse me. I would like to move on. I know we have got a number of other questions here.

MR. JASINSKI: Since you're a product formulator, I just want to make sure that--and you are saying you are a responsible company--the question I have--and see if my understanding is very briefly--the herbs are grown by people some place in Asia. You nor nobody from your company monitors the growing of these herbs or how people treat these. They are put together.

You buy them, what on bid, in this country so you

don't know what you're buying; and there is no monitoring of this and there is no series of analytical chemical methods that you can do to assure the safety or the quality of this. And then from Dr. Love's presentation--I don't know about yours--but then we have varying amounts of ephedra alkaloids and other sort of active alkaloids in these preparations.

Is this the case?

MR. GISSEN: Well, I meat that's kind of a cursory explanation. It varies greatly. There are companies that are very reputable that sell high-quality herbal products, many of which are--

MR. JASINSKI: No, I'm asking about your company. How do you assure that it's a high quality herbal product? To do that you would have to monitor the growing of this and who grows it.

MR. GISSEN: No. All you have to do is monitor the end product and basically make sure that the product is properly analyzed. I mean basically we have the same problem as people that are selling black pepper in the supermarket. You know, that's grown in another country, and it's shipped here in the cargo hold of a ship in sacks and the product--

DR. LARSEN: I don't think we're making much progress here.

MR. JASINSKI: No. It's inconsistent with what you're saying. The issue is--we're not talking about black pepper--I just want to make sure that you're not monitoring the end product, and if you are talking about things--you raised the point there might be contaminants for which you have no chemical analyses and no way to--

MR. GISSEN: No, no, I didn't mean there are--

MR. JASINSKI: And the only way you can do this is to assure that the product, itself, is safe and nothing is added.

MR. GISSEN: Certainly if--I am sorry.

DR. LARSEN: I really would like to move on.

Dr. Ziment?

DR. ZIMENT: Yes, I just wanted to ask one question. When you say there are serious side effects, including suicides, from established ephedrine products, are you quoting opinion or verifiable fact that is put out by the Poison Control Centers?

MR. GISSEN: That there have been suicide attempts using ephedra products, is that the question?

DR. ZIMENT: Well, you said that ephedrine products have been used in suicides.

MR. GISSEN: I was just testifying in front of the Texas Department of Health, they had a case of somebody that

took 95 25-milligram ephedrine sulfate capsules in a suicide attempt and other than a two-day stay in the hospital the person completely recovered.

DR. ZIMENT: But is there more than one case?

MR. GISSEN: Oh, there certainly is more than one case.

DR. ZIMENT: And are they reported to where we could verify it in the literature?

MR. GISSEN: I couldn't personally point you in the direction but I'm sure that both the FDA has cases of people and certainly I know that emergency room physicians have to report suicides to some reporting agency. So, there should be a pretty good compendium of the total number of attempted suicides that are recorded each year that are known to be due to ephedrine or ephedra.

DR. LARSEN: I would really like to move on now, please.

The next speaker is Mr. Stephen Shapiro of Bass and Ullman in New York.

MR. SHAPIRO: Good morning.

My name is Stephen Shapiro from the law firm of Bass and Ullman. I am appearing here today on behalf of a number of distributors and retailers, all of whom responsibly market and distribute dietary supplements which

contain ma huang, also known as Ephedra seneca. Rightfully, there is a concern about the possibility of alleged adverse reactions associated with the consumption of food products containing ephedra alkaloids. Where there is a possible connection between consumer products and adverse reactions it is always appropriate to proceed with caution and the utmost care.

At the same time, however, we must not lose sight of the possibility that the reported consumer injuries may be the result of misuse rather than correct use. Also, looking at emergency room statistics, I would like to point out that the enormity of the reports of misuse of such products as aspirin, acetaminophen and ibuprofen should be of a far greater concern.

We are here today in support of ma huang products and ma huang extract products which contain only naturally occurring ephedrine alkaloids. As we are all well aware there are hundreds of dietary supplement products being sold which contain ma huang and it is clear that these products are widely sold and consumed by large numbers of people.

The estimates that I saw were that on any given day at least 5 million people consume a ma huang containing product. Obviously we have heard estimates both higher and lower and I cannot give you an exact number.

But with such a long and wide history of use there is a need to have a thorough understanding of the basis and underlying facts between the alleged adverse reaction reports which are constantly being cited and which are of comparatively recent origin. For example, how many reports are for insomnia, an expected effect not an adverse reaction which can be remedied by simply not taking the product late in the day? How many indicate product abuse? How many contain insufficient information to determine what the cause was?

The special working group of the Food Advisory Committee of the Food and Drug Administration met in 1995 and determined that at least many of these anecdotal reports of injury do not withstand scrutiny. The special working group concluded that ma huang products do not present a significant or unreasonable risk of harm when sold with conservative dosage limitations, accurate label information and adequate warnings.

We agree with the findings of the FDA Working Group and submit that ma huang, when responsibly used, and appropriately labeled is safe for consumption as a food and as a dietary supplement.

Any complaints that our clients have received regarding their ma huang products have been minimal and

uneventful and are primarily the reports of insomnia which are remedied by telling the individual not to take the products after 4 o'clock in the afternoon.

Until recently there was a question whether warning labels could properly be placed on dietary supplements. This issue was resolved when Congress passed the Dietary Supplement Health and Education Act of 1994. The Act, among other things, amended 21 U.S.C. Section 343, to add the following: "A dietary supplement shall not be deemed as branded solely because its label or labeling contains directions or conditions of use or warnings." It may be that ma huang was one type of dietary supplement that Congress had in mind when it said that warnings included on dietary supplement labels shall not per se render a product a drug.

Clearly it was contemplated that some dietary supplements could have potential side effects and that warning statements would be appropriate. We respectfully ask the Food Advisory Committee adopt the recommendations of the special working group. There is still no justification for taking any different action at this time.

There has been an overreaction of reports of incidents which repeatedly have been shown to be the result of something other than the responsible consumption of a

food product containing ma huang or ma huang extract.

Most food products can be safely used and consumed by the vast majority of the population. Some widely consumed food products, however, can have serious side effects in some individuals. Dr. Jones, yesterday, discussed cases of uncooked chicken. There are also people who have severe reactions to such common products as peanut butter, shell fish or dairy products, yet, these can be sold without restrictions. Aspertame and olestra have caused adverse reactions and they can be sold for use in food with an appropriate label statement.

We would also briefly like to make a point concerning the widely reported death of the college student in Florida on spring break. It is tragic that a young person died. However, it has also been widely reported that the individual ignored clear warnings on the product and took at least twice the daily dose all at once. Those same reports indicate that his companions all took three times the daily dose without incident. In addition, according to the police report, cannabis and another product, Nexus, consisting of the herb kava-kava were found in the hotel room.

It is noteworthy that the autopsy report contains no findings at all relating to the presence of other

substances such as cannabis, cocaine, amphetamines or barbiturates. It appears that no tests were performed for the presence of these and other substances which is most certainly very strange.

Yesterday, Dr. Love said that the tests were performed. If so, the results were not made a part of the autopsy report. Is there any further information that FDA could supply? Has this information been supplied to the members of the committee?

With that in mind, can it be stated with any degree of certainty that ma huang was the sole cause of the death in question? I raise the question, I don't have the answers.

The Ad Hoc Committee on Ma Huang Safety submitted to you as part of their package the declaration of Dr. Joseph Brazelica, a toxicologist, which sets forth many deficiencies in the autopsy report and concludes, "That it is not possible to determine from the report of autopsy to a reasonable degree scientific certainty that the cause of death was the ingestion of some quantity of a product containing ephedrine."

In addition, an FDA spokesperson, Judith Falk, has been quoted in newspapers as saying, "There has already been one death directly related to taking more than the labeled

dose and there were 15 other deaths associated with the use but the causality has not yet been established."

DR. LARSEN: You have about one minute.

MR. SHAPIRO: Okay. We must question whether any incident has been directly related to a ma huang product and appreciate FDA's acknowledgement that causality has not yet been established.

Certainly any death or serious incident is of enormous concern and a great tragedy. They are not to be trivialized. Yet, we keep hearing that the deaths are "associated with the use of ma huang products." Associated. I'm not a scientist or a doctor, I'm not sure what that means.

In closing, nothing has changed since last October and there is no reason to believe that the Special Working Group's findings are not as valid now as they were when they were first made last year. We ask that FDA consider all factors before taking any action which would unduly restrict the sale of the extremely popular and safe dietary supplements products.

Thank you.

DR. LARSEN: Thank you.

DR. CLYDESDALE: Excuse me, could we have clarification on that autopsy report?

DR. LARSEN: Could we hold that question until we get to the discussion?

DR. CLYDESDALE: Surely.

DR. LARSEN: Thank you.

Mr. Gordon Peterson from Eola Products, Inc., St. George, Utah.

Again, please record for the record your name and affiliation and since, for some reason my little stop-light timer has gone out on me, I will be timing you and letting you know by the microphone.

MR. PETERSON: Thank you.

I'm Gordon Peterson and I work in the nutritional supplement industry. My background of education is I have a bachelor's degree in biology/chemistry, a master's degree in cardiac rehabilitation therapy and my doctoral work is in medicinal toxicology where I studied natural products.

Before I took employment in this field, for my own conscience I needed to know that these products were safe. Here are some facts that convinced me that ephedrine, ephedra could be safe and to what levels? I hope these facts can be beneficial in your process of making up your own mind.

I'm just going to walk through the process I went through to convince me of what level ephedrine can be safe.

I first decided to look in the most credible medical textbooks I could find so I went to the Merck Manual and I found that the LD-50 or the lethal dose 50 or the dose at which it takes to produce a death in 50 percent of an animal group was 650 milligrams per kilogram in rats. And I then decided I would look at what is considered the pharmacological bible, Goodman's and Gilman's, in their book, Pharmacological Basis of Therapeutics, and found ephedrine listed as follows and I quote:

"The usual oral dose is 25 to 50 milligrams repeated every three to four hours for a 150 to 300 milligrams per day dose." I then decided to take an approach that the physicians might take and I looked in the American Hospital Association's Hospital Formulary which recommends the following:

"The usual adult dosage is 25 to 50 milligrams every three to four hours." That's a direct quote. Another quote from this American Hospital Association's Formulary is as follows and I find this to be as valuable to this discussion as anything else and I quote:

"For self medication in children 12 years old and older, the usual dosage is 12.5 to 25 milligrams every four hours." Let me repeat that, for self medication in children 12 years old, ephedrine is found to be safe at 12.5

milligrams to 25 milligrams given every four hours.

Mind you, this is based on clinical trials and proven by physicians over time. It goes on. In the Hospital Formulary, it also states: "For children 6 to 12 years of age, ephedrine is safe at 6.25 to 12.5 milligrams every four hours."

It goes on: "To be safe in children two years of age they may receive 2 to 3 milligrams per kilogram of ephedrine in four to six divided doses."

I just want to remind you that this has been demonstrated to be safe in children two years of age and at the 25 milligram level for self medication in children.

I then decided I wanted to make a review of the medical journals that were available so I went through the medical journal study and I found in an article published in the Journal Allergy and Clinical Immunology 1988, it was written by two Ph.Ds, and seven medical doctors among others. In their study of 373 pregnancies, taking ephedrine, ephedrine use was found to be safe.

It goes on and says no complication or congenital malformations were found and it was noted that no other problems occurred. There are few substances that have demonstrated or proven this level of safety.

Another study. This one comes from the

International Journal of Obesity 1993, and I quote:

"We conclude that the ephedrine/caffeine combination is safe and effective in long-term treatment in improving and maintaining weight loss." It goes on, another direct quote:

"The side effects are minor and transient and no clinically relevant withdrawal symptoms have been observed."

Another study, ephedrine is not very toxic. The minimal fatal dose being 100 to 145 milligrams per kilo in rats, smaller doses were apparently harmless.

Now, the interesting thing about this is that it comes from the Journal of Pharmacology and Experimental Therapy and was published in 1924. Ephedrine has been published to be safe and the level to which it is safe since 1924.

By the way, 97 percent of ephedrine is excreted in 48 hours. That comes from the European Journal of Clinical Pharmacology published in 1975.

After the medical literature review, I still wanted to know if ephedrine was safe. So, at the request of the company I worked for at the time, I asked if I could do a study myself. By the way, the study is published and it's found in Fundamental And Applied Toxicology, Vol. 30, page 111, published March 1996. This is current literature.

And in this study I tried to find the most credible laboratory possible. I chose Utah State University and the principal investigator was Dr. Robert Sidwell, a former chairman of the National Institutes of Health and he's presently NIH-funded.

In this P-3 laboratory, he performed a toxicology experiment on our dietary supplement containing ephedrine. The reason why I did that was because I didn't want to base it on ephedrine in any other form than the exact form we were giving.

The results are published and they are as follows: The LD-50 for ma huang powder extract in BALB/C mice is 4,000 milligrams per kilogram per day. The LD-50 for ephedrine alkaloids in ma huang in mice was 360 milligrams per kilogram per day. The LD-50 for the plant, ma huang, would be about 1998 milligrams per kilogram per day.

If you used the formula derived by Dr. Frierich at all, published in Cancer and Chemotherapy Reports, Vol. 50, published in 1966, to calculate the quantitative toxicity data, based on surface areas between mice and human species, you find that the LD-50 for ma huang powder extract is calculated to be 333 milligrams per kilogram per day. And for ephedrine alkaloids in ma huang it is 30 milligrams per kilogram per day.

Now, to put all of that--

DR. LARSEN: Can you please wrap it up?

MR. PETERSON: Yes, I'm sorry. To summarize that, this means you would have to take at least 300 capsules of the exact product we're selling to find an LD-50. Basically I believe these are facts based on published scientific studies, clinical trials and medical formularies and they validate the decision from the Ephedra Working Group of last year which is that 25 milligram dose or 100 per day of ephedrine is safe and is published to be so even in self-medicating children.

In summary, 25 milligrams is published to be safe during pregnancy, to developing fetuses, in combination with caffeine, in children, and in self-medicating children and has been proven to be so since 1924.

Thank you.

DR. LARSEN: Thank you, one question.

Dr. Georgitis got his hand up first.

DR. GEORGITIS: Your quotations about the dosing in children is correct, but do you understand that this is for a specific condition? And, in addition, you need to be aware that children do not self-medicate themselves, the parents give them the medication.

MR. PETERSON: Yes, sir. And I apologize if I

misled you. I did not intend to do so. I just tried to make this as short and concise as possible.

DR. LARSEN: Okay, I will let Dr. Hui and then Dr. Applebaum and then we will go on to the next speaker.

DR. HUI: I felt that what you have put together is very useful for us but these are literature written for professionals by scientists and it's used to treat diseases. There's nothing that's really safe. I think it's all risk-benefit ratio. For, you know, the patients that really have a life threatening disease, the doses used are relatively safe but it's not safe. It can still lead to side effects and I think we will need to take this into consideration.

DR. LARSEN: Thank you.

Dr. Applebaum?

DR. APPLEBAUM: Mr. Peterson, I was just wondering if you would comment on the metabolic profiles, the similarities or dissimilarities between the mouse and human?

MR. PETERSON: I'm not sure exactly what you are asking for. In the interest of time, I would suggest that we look at the most important thing, that it was demonstrated to be safe at a certain level. The metabolic similarities have been demonstrated to be similar in the immune system and some things in metabolic have definitely been different from mouse to humans.

So, yes, there is a question as to whether they are exactly convertible from mouse data to human data but in the interest of not having to perform a human LD-50 the mouse data is a close approximation.

DR. APPLEBAUM: No, no, I'm not suggesting an LD-50 for humans. I'm just wondering in terms of the suitability of the species to extrapolate from the mouse to man in assessing the LD-50.

MR. PETERSON: I thank you for bringing that up. I referred to Dr. Frierich in his publication in Cancer and Chemotherapy Reports 1966, where he published and it has been accepted to the medical literature, the ability to convert by the factor given in that study from BALB-C mice to humans and the formula by which you do so.

DR. APPLEBAUM: But was ephedra the chemical that he was alluding to?

MR. PETERSON: Oh, no, it's a generality. And I appreciate that comment. It is, in fact, a generality meaning when people convert basic doses from human to mouse or to rats or to horses there is a generalized conversion rate to do so.

DR. APPLEBAUM: No, no, but my question is, is the mouse similar enough to man to permit you to make that extrapolation?

MR. PETERSON: Oh, the BALB-C mouse has been demonstrated to be as comparable to man in many different situations. In fact, it may be one of the if not the most used animal for that purpose.

DR. LARSEN: May we move on?

DR. CLYDESDALE: I just wanted to clarify that the numbers you gave are all based on the compound being treated and considered as a drug, correct?

MR. PETERSON: Most of the numbers were, yes, sir, except for the experiment which I performed with Dr. Sidwell.

DR. CLYDESDALE: Right. And that would assume then that if it was treated as a drug that it would be regulated as a drug. So, the safety numbers they came up with are based on an assumption that the compound in question is regulated as a drug, is that correct?

MR. PETERSON: That would be correct.

DR. CLYDESDALE: Thank you.

MR. PETERSON: I was just trying to demonstrate a safety level by which you might gauge some level of fact.

DR. LARSEN: Thank you.

I want to move on to the next speaker but this is for you if, while we are working with the next speaker, if you have these LD figures in hard copy, if you could provide

them to the staff to make copies for the committee.

MR. PETERSON: I will do so.

DR. LARSEN: Thank you.

The next speaker is Dr. Calvin McCausland from Enrich International, Orem, Utah.

DR. McCAUSLAND: Thank you.

I work for Enrich Corporation. I am a graduate of Brigham Young University in Provo, Utah, in the area of chemistry and I am also a Lt. Col. in the United States Air Force, a scientific officer. That is in reserves.

It is a great tragedy, in fact, it's listed as the greatest tragedy if one loses one's spouse. That can be compounded when it's in the prime of life, 36 years old, a perpetual bride, with five children aged 3 to 11.

It's heart-wrenching to look into the fact of a child full of tears asking about mom. Where is she? I am a man acquainted with grief. My wife died not of abuse, she died as the result of a chemotherapy incident to cancer. And I would not trivialize the loss of anyone. But objectively, science must detach themselves somewhat from emotion and look at the facts, the scientific facts.

And if you look at the 20-year old in Florida and the autopsy report, you will find reasonable doubt. That reasonable doubt has been spelled out by Dr. Borzelica, from

the Medical College of Virginia and it's in those three volumes that you have before you.

There are other deaths that have been listed that have reasonable doubt. They took ephedrine a week before, reportedly. There is none in the tissues of the autopsy. Reasonable doubt.

The one in Boston did not have a chance to have our experts look at--someone playing tennis who died of an infarction. The head of regents at the University from which I graduated, made this following statement with regard to sickness. "We should do all we can for ourselves first. Dieting, rest, taking simple herbs known to be effective."

That's the wisdom of a sage. He goes on later, before we turn to our skilled and helpful men who can help us so wonderfully with their powerful medicines. Science is the pursuit of fact. Politics is the pursuit of compromise. Elizabeth Yetley has asked you to determine on the facts, the scientific facts. And the fact is that dietary supplements are more than foods. That's why we have this new law called Dietary Supplement Health and Education Act, seeking protection under that law from bureaucratic abuse that has occurred in the past. And the fact that herbs have therapeutic value is well-known and commonly known.

Ephedra is no exception. You could pick any of

800 herbs and be here on the same thing, and pepper would be included. Our company does sell ephedra. It's not our major product, it's not even the bulk of our product. Actually we have several products in that category.

We sell products in Canada, Micheline Ho is not a name unfamiliar to me. And we have drug identification numbers for those products. We do GMPs. We do assays. We assay the amount of ephedrines by high performance liquid chromatography. We test for bacteria with the ELIZA method, that's the enzyme-linked immuno-assay.

I would like to say something about support. Remember Dietary Supplement Health and Education Act got more support than any other issue, more letters sent to Congress supporting the general people supporting that. Maybe because in the findings of that Act, it says, 50 percent of the 260 million population use vitamins, minerals and herbs or what are now known as dietary supplements.

And in Ohio, where they did legislate against it, I would like to make one remark. We have proposed legislation there and it has now passed the house, exempting Chinese ephedra and its concentrates, and it passed the house 87 to 7. The people once again made a point.

I have met K.K. Chen. He's the individual who took ephedrine from ephedra and made it a drug. We need to

look back the other way. If that is where it came from, is it still not a safe herb or an effective herb I meant to say.

Now, I would like to refer back to Dietary Supplement Health and Education Act because the burden of proof in Section 4 places the burden of proof squarely on the FDA. And this applies to ephedrine and ephedra in dietary supplements.

I have noted, during these hearings, a lot of politics and not too much science. The LD-50 of 650 was not even given. The information from the formulary concerning two year olds and no one has explained the fact that three milligrams per kilogram is allowed for children as opposed to .7 for adults. I mean why the descending amount.

You asked about the mouse model. Yes, there is differences in the enzymatic processing of ephedrine by mice and men but that does not compromise the data that much. The whooping cough tested in China in 300 children ages three to five, it was found to be very effective.

The monograph from the FDA suggests that 50 milligrams a day, 150 per dose in the assay, that's where the data came from. The numbers are there, they were there in the past. They are still there. What changes is compromise. The facts don't change.

Mr. Fong even reported that three grams is the traditional herbal method. Three grams at 1.5 percent is 45 milligrams per dose, per day. Whatever, I'm not sure what exactly it was reported there, but 45 milligrams. And I support the Working Group's last conclusion, 25 milligrams per dose, 100 per day.

There's a dilemma here. If you reduce it to a point of safety then you lose efficacy and the industry loses customers for reasons that it no longer works. And, yes, I'm saying that they are efficacious, and I think third-party literature is allowed in the FDA indicia.

And I do have some numbers with regard to the exposures and what that means in people days but I'm out of time and if you would like to ask me that question I would welcome it. But I would like to remind you again, Section 4,: "The safety of dietary supplements and burden of proof on FDA." That's where the burden of proof is. That's where you need to hear it from.

Don't let them, you know, they're asking well, have industry give us the information. There's been a paradigm shift, gentlemen, the paradigm shift is now here is where the proof has to come from and I've heard gross negligence in terms of lack of references, including the safety evaluation right here--conclusion, the majority of

adverse events appears, and there is not one scientific reference in here. There are scientific references and they are being ignored. Science is the pursuit of facts.

Thank you very much.

DR. LARSEN: Thank you.

One question. Thank you.

We have two more speakers and I think what I want to do is try to get through the two more speakers and then we will take the mid-morning break.

The next speaker is Mr. Bill Appler, the Executive Director from the Ad Hoc Committee on the Safety of Ma Huang.

Mr. Appler, you have a presentation that's going to take about seven and a half minutes. And you're the person that had the letter from the gentleman that I overlooked, Dr. Graham Patrick. How long do you think that would take you?

MR. APPLER: If I were to add the remarks that I have to make because of that confusion, I think it would probably extend to about 10 or 11 minutes with your indulgence.

DR. LARSEN: Okay.

MR. APPLER: Thank you very much.

I'm Bill Appler co-chairman of the Ad Hoc

Committee on the Safety of Ma Huang Ephedra Herb. The committee was formed in April of 1995 when the State of Texas first proposed to restrict the sale of dietary supplements containing ephedra herbs. The proposal was later withdrawn.

Our committee is unique because we have focused our efforts solely on developing and disseminating the traditional forms of safety and toxicity data that bare on the safety of any ingested food ingredient. To that end, we commissioned two separate independent scientific literature reviews on ephedra herb and ephedrine. We reviewed the National Toxicology program animal studies on ephedrine done in 1986. And we commissioned an original animal study on a typical ephedra herb product, nephogen in rats, mice and dogs, all which are negative. And we subjected to careful independent written toxicological review first the FDA's 1994 health hazard analysis; second, it's the 900-so-called Texas injury reports reflected in the material that Ms. Culmo discussed yesterday. We also had toxicologists look at three of the most prominent deaths that have been publicly associated with the products--the only two mentioned in the health hazard analysis by FDA and the two mentioned last week by the Center for Disease Control, as well as the Peter Schlendorf matter which has brought this

matter to the forefront again and other materials baring on injuries.

We also commissioned a retrospective study of 235,000 Canadian users of a typical ephedra herb weight loss product to evaluate whether the reported results in Texas would be seen when you looked critically and directly at the results of ephedrine ingestion.

The results of our work in three volumes, about 1,500 pages, was submitted to the committee last year, as you will recall. This year, for your consideration we have given you an expanded, revised, with additional material and most hopefully more user-friendly form of some of these materials. We believe they show that when taken in accordance with recommended doses and labeling, ephedra herbal products, primarily sold for weight loss, energy and, to some extent for performance enhancement, are safe at the levels this committee recommended or, at least discussed, I think more properly last October.

Vol. I contains our expert's review of the adverse injury reports and the alleged deaths. We had agreed with Mr. Young of NFA quite a while prior to this meeting that the doctor who spoke yesterday would look at the FDA reports with less emphasis on Texas and our toxicologist would look at the Texas reports. Those reports are in the Appendix as

A and B and No. 1.

Vol. II contains the two separate scientific literature reviews we commissioned. Vol. III contains a summary of the NTP animal studies as well as our own animal studies.

These all contain a speaking index. That is an index which summarizes each document in the volume. We have made these indexes and Dr. Patrick's recent review of the new Texas data available in the colored folders we put outside for members of the public or anyone who would care for that. If you would like to see our full report which we distributed to each committee member, see me if you would like to get that.

Against this background I hope to offer today, in the brief time allotted to the committee and to Dr. Patrick, some explanations and interpretations of the scientific evidence that our committee has gathered which we hope will aid you in reaching a consensus recommendation to the Food Committee and then to the FDA. On the whole, it is our recommendation that you adopt as soon as possible the consensus recommendations reached at your October meeting and reflected in Dr. Larsen's minutes, supplemented as you may think appropriate by some of the consensus suggestions, additional suggestions made by the industry yesterday.

And I just want to urge personally and somewhat parenthetically the need for this committee and the full committee in the FDA to move ahead with these recommendations because, as you know, the industry is eager, willing and moving ahead on its own program of implementing regulations.

A number of the products on the table yesterday contained labeling that is no longer in use. For example, a nephogen product, the product which was tested in our studies, now contains labeling indicating how many milligrams of caffeine and how many milligrams of ephedrine are contained in each dose. Very specific information of the sort that the committee would like to see. It also contains extensive warnings which were not on the bottle that were collected last year because they were not on the bottle at that time.

It seems to me that the basic principle of toxicology is dose makes the poison. And it reflects the fact that almost any chemical is safe at some level and hazardous at some level. So, caffeine, while viewed as the safe food ingredient, sends thousands of America's to emergency rooms for treatment every year. Caffeine, niacin, and other safe food ingredients cause numerous adverse reactions.

For example, in the Texas reports of 900 injuries, the largest single category of injuries is reported to be niacin flush a response not to the ephedrine but to the fact that when the product was reformulated, niacin was added to it apparently in higher doses than might have been ideal.

So, one-ninth of those Texas injury reports, 900 reports, are niacin-flush related reactions which probably--and I say this advisedly--probably have very little to do with the ephedrine.

Traditionally toxicologists begin to assess possible risks from a dietary supplement by looking at any existing FDA or other requirements for that ingredient. In the case of the ephedrine component regarded as the most active in an ephedra herb product, FTC's OTC monograph declares that for use by health-compromised asthmatics, including myself, ephedrine ingestion is safe when sprayed into the bronchial tubes in 25 milligram single or divided doses and is safe up to 150 milligrams per day. I didn't bring my atomizer with me but I have used it off and on for perhaps the last 20 years for mild asthma.

While there is a proposal mentioned in passing yesterday to withdraw ephedrine from that status, the introduction of that proposal explains that the reason for the proposal is DEA's concern about diversion of ephedra

into illicit drugs. I find it difficult to believe on any scientific or toxicological basis that my ingestion by inhalation in a health compromised population, 25 milligrams single dose, 150 a day, is safe as declared by FDA and its experts. But that oral ingestion at the levels you recommended last October 20 milligrams of ephedrine alkaloids, 25 total alkaloids, AD/100 per day, is possibly the hazard that FDA has tried to present it as.

If that were so, we would be seeing literally thousands of injuries among the tens of millions of daily users of bronchodilator products. Needless to say, despite the far more sophisticated system FDA has for capturing drug reactions, no such substantial reports for bronchodilator use have appeared.

After the sort of preliminary review, the mentors who taught me much of the food toxicology I know--Dr. Bernie Ozer--now deceased--Dr. Joseph Borzelica, individuals well-known, frequently used by the center, Dr. Shank and others, as experts explained to me the next source of information on possible risks from a food or food ingredient is the scientific literature concerning that ingredient. So we commissioned what is almost certainly the most comprehensive reviews of the literature on ephedra herbs and ephedrine ever conducted. They run to about 100 pages in Vol. II, and

we included several hundred of the original articles in the volumes we gave you last year so you could look up the articles and confirm that it says what the author of the review says.

Significantly, the review of adverse events presented by FDA yesterday did not back up its asserted harm from ephedra products at the low dosage you recommend with any supporting literature.

Indeed, you will recall from Dr. Love's presentation what you will recall are three slides, seeking in advance to undermine the importance of the several dozen weight loss studies discussed in the literature reviews, studies conducted at single doses of 44 to 50 milligrams of ephedrine for up to 26 weeks with no reports of any serious adverse effects.

If, as FDA claims, there are examples of otherwise healthy young men and women suffering serious or fatal adverse incidents upon first taking or shortly after first taking this product it is inconceivable that the same effect would not have shown up sometime in some clinical study or elsewhere in the literature.

DR. LARSEN: Can you make the transition to the letter?

MR. APPLER: Shortly.

If you can give me 30 seconds. Dr. Love's point in this regard yesterday was that the inclusion criteria for clinical trials may screen out those who are at greater risk for adverse events but, first if that is so, then the clinical patients would be precisely the kind of remaining patients in which these adverse events are supposedly seen.

Second and far more importantly is the industry was urging FDA to provide labeling on these products so that those who should not take them will be excluded. We urge the committee to do that.

A fair summary of the literature is in Pentel's article, Toxicology of Over-The-Counter Stimulants, JAMA, 252, 1898-1903, 1984. Dr. Pentel concludes: "Toxic effects may result from over-dose, drug interactions or a disease that causes increased sensitivity to these products."

Over-the-counter formulations may contain up to 30 milligrams of ephedrine and doses up to 60 milligrams generally do not increase blood pressure. Doses of 60 to 90 milligrams produce only small increases in heart rate.

I will skip over the material on the animal studies which is in our reports and that brings me to the results of our review of the Texas cases.

This is what Dr. Patrick would have presented.

The concern with ephedra herb does not seem to

rest on either the scientific literature, reports of incidents there, clinical studies of ephedra or ephedrine--there was one study done in the literature on the ephedra product, itself--nor, upon animal research identifying any risk. The FDA's drug center continues to allow health-compromised asthmatics, like me, to inhale 25 milligram doses up to six times a day.

The only thing supporting any concern about ephedra dietary herbal supplements are these injury reports collected by FDA, more than 40 percent of which originate in the State of Texas. As you may have observed or may have picked up from Ms. Culmo's presentation yesterday, these reports have allegedly been reviewed or more correctly summaries have been reviewed by the Texas Medical Association by a panel of doctors in the Department of Health.

The reports of those two groups state that they reviewed over 900 incidents and that number is roughly equal to what Dr. Patrick saw down there when he reviewed it. The problem is that the Texas results, including 900 cases, begin with 300 cases for Formula One which are based on the fact that under the settlement agreement between Texas and Formula One, Formula One is required to report to the State any time a product is returned for any purpose that might in

any conceivable way be a health risk.

If I may for a minute read you some of those 300 cases treated by the Texas Medical Association as adverse injury reports. Page 5692, so you can identify what I'm talking about, I read articles put out by the FDA and the customers would not take the product after reading this article, therefore, I'm returning it. That's one of the 900 reports.

I returned it because of mild headaches and news releases. 5735, there was a news bulletin on Channel 4 that told of serious side effects. 5737, I read an article in the paper that caused me to remember I had once had toxic reactions to the products. If you go through Dr. Patrick's more detailed analysis in sub-A of Vol. I, I think you will find a great deal of concern about these 900 reports.

My personal concern is how any physician could look at those and say, well, there are 900 reports of injuries.

The next block--and it 100 of those 300 are niacin rush--the next block is 400 reports sent in by the Texas Poison Control Centers. Let me summarize one of those, although Dr. Patrick points out, they are virtually all for OTC products that, under the Texas proposal, would remain on the market.

The two reports from 1996 are the North Texas Poison Control Center reporting a total of 94 incidents reported to that center during calendar 1996, the current year. And 22 of those were for OTC products, such as No-Dose, the largest particular product identified. And 66 were for Mini-Thins, a product consisting entirely of ephedrine sulfate, I believe, in 25 milligram doses unlabeled.

That means of the 94 reports in the Poison Control Center for North Texas, there were exactly two that were related to herbal and two others related to ma huang. In every one of those cases, as Dr. Patrick points out, there was no permanent injury of any sort and all the results seen there were mild. So, that takes care of 700 of the 900 Texas reports.

His report goes on to explain the others. The largest portion of the others and almost all the critical ones are what are called in Texas TDPA reports. Before you may sue a company over its product, you must send them a letter saying that you plan to on behalf of whom.

None of these letters indicate what the condition is other than the patient was somehow injured. The fact of the matter is that the reports in Texas--and I encourage any of you to do down there and look at them--are absolute, if

not fabrication, at least very, very over-hyped to this committee.

And that was not--

DR. LARSEN: You've had nearly the full time for two speakers, can you wrap it up, please?

MR. APPLER: All right. I would like to close just making two points. Your device center of FDA is having a conference on the 21st of September on a topic called Denominator Data. Since reports of injuries have to be filed under the statute for medical devices, the center is concerned that it can't evaluate the meaning of enumerator, so many injuries, without knowing what the denominators are.

We don't really know the denominators here, but the number of reports in the summary material from the center was 604 when we started, minus the six cases from Mr. Betz that didn't involve ephedrine products. While some of the comment was going on before, I would just like to add, I went through that. One of the panel members said there were 30 reports of death, 30 people had died. Well, in fact, there are only 21. This is a difference of almost 50 percent.

More to the point, most of those are related obviously to other conditions as you were told yesterday. As far as the suicide question someone had, there are

several reports of suicides in that book. People attempted to kill themselves with these products. Page 65, 10378 is one of them.

Finally, a number of reports, the two quick ones, I note, 10067 and 10075, there is no adverse event noted. The report specifically says, no adverse incident reported.

The reports that are in there include multiple sclerosis, ALS, menstruation in a 75-year old. The ones I found interesting, one individual complains of a sustained erection as a result and one complains of impotence.

So, if you go through those with any care at all you can knock about one third of them off without even being a physician. And we would suggest that--

DR. LARSEN: Would you please close down, please?

MR. APPLER: We suggest, therefore, the committee's concern is very appropriate with regard to labeling. We urge you to move ahead and adopt the proposals that you discussed last October.

Thank you for your time and your indulgence.

DR. LARSEN: Thank you.

One question, Dr. Ziment?

DR. ZIMENT: Just one question. You, Mr. Appler, suggest that ephedra is available as an inhaler?

MR. APPLER: Yes, sir.

DR. ZIMENT: You say you take it yourself. Is this an over-the-counter product or is this a marketed product, generally available?

MR. APPLER: This is an over-the-counter drug product under 21 U.S.C. 341 the cough, cold, allergy and bronchodilator monograph. The agency has provided these products may use ephedra as an effective bronchodilator in doses of up to 25 milligrams per dose at 150 per day.

I put a copy of that regulation on your desk this morning.

DR. ZIMENT: But is it available as readily purchased?

MR. APPLER: Yes. You can walk in a store and buy it. You don't need to talk to the pharmacist.

DR. ZIMENT: For the treatment of asthma?

MR. APPLER: Yes.

DR. ZIMENT: For the treatment of nasal problems?

MR. APPLER: No, it's for asthma. It's for shortness of breath. It's to dilate the bronchial tubes, normally secondary to an asthma attack.

DR. ZIMENT: Thank you.

DR. LARSEN: I would like to move on to our last speaker now.

The last speaker on the open public hearing is Mr.

Blaine Wilson, consumer. He's program director for the Cardio-Pulmonary Rehabilitation Institute at the University Medical Center in Lubbock, Texas. But he is appearing as an individual consumer.

MR. WILSON: My name is Blaine Wilson and I am program director of the Cardio-Pulmonary Rehabilitation Institute at University Medical Center in Lubbock, Texas.

I am speaking on behalf of myself, my wife, and my family. First of all, I want to tell you what I'm not. I'm not an attorney. I'm not a lobbyist. I'm not being paid to be here. It's costing me $150 per minute for the privilege to get up here and talk to you today.

What I am is a health care professional. I have an undergraduate degree in exercise physiology, a master's degree in cardiac rehabilitation and primary prevention. I'm a member of the American Association of Cardiovascular and Pulmonary Rehabilitation. I'm a certified preventive and rehabilitative exercise specialist by the American College of Sports Medicine.

One year ago today, my wife was lying in the hospital after suffering an adverse reaction to a dietary supplement containing ephedrine or ephedra. What I would like to do briefly is read a part of the Morbidity and Mortality Weekly Report dated August 16th. My wife is

patient number three in that report and I believe all of you have a copy of that.

On August 17, 1995, a 38-year old woman with no history of seizures experienced two petite mal seizures beginning at 11 p.m. She experienced two additional petite mal seizures the following morning and in that afternoon had an onset of a generalized tonic clonic seizure lasting approximately two minutes, during which she required respiratory assistance.

On August 17th, she taken two tablets of an ephedrine containing dietary supplement at 10 a.m. and two more, five hours later, as directed on the product label. This is true. The product label actually directed her to take two to three. She is conservative and only took two.

During August 19 through 22, she experienced five additional episodes of unresponsiveness while sitting or standing. While waiting in the office of a neurologist, she sustained an additional generalized seizure witnessed by the neurologist and staff.

She was hospitalized for monitoring, treated with anti-seizure medicine, and diagnosed with new onset of tonic clonic seizures with complex, partial seizures. Other possible causes of seizures were excluded. She was discharged and was advised to avoid any medications or

products that contained ephedrine, pseudo-ephedrine, or related drugs. Since discontinuing use of this product she has had no additional seizures.

My wife has no pre-disposing conditions for seizures and she is not an obese rat. Most of the studies that have been cited are on rats and obese people. You can't take those studies and put it over the general population, that's not good science.

Yesterday, Dr. Kessler asked you when you make your decision to take real people in mind. Well, here I am.

My wife has not had any seizures since leaving the hospital last year. She has discontinued her anti-seizure medicine. That was in February of this year. She has had multiple sleep-induced EEGs, they were slightly abnormal after her seizures. Happily to report, her EEGs are normal now, off of medicine.

She did not take the product for abuse. Again, she took it as directed by the label. This has got to stop.

Dr. Love said yesterday, 14 percent of the adverse reactions come from the first dose or first day. So, why don't we take this part of the table and just push it back. That's about 14 or 20 percent of the advisory committee.

How many of you have 14-year old daughters? I do. Do you think it's safe for your daughter to take these

supplements? That's a decision you are going to have to make.

Are you going to let the attorneys and the lobbyists make a scientific decision for you? Certainly, I hope not. How many more bodies need to pile up?

In closing, I would like to submit a letter from Congressman Larry Combest of the 19th District in Texas and briefly it states, "Mr. Wilson's wife suffered multiple seizures after ingesting an ephedrine supplement, as directed by its label. It is my understanding that several cases similar to Mrs. Wilson's have been reported to the Food and Drug Administration as well as the Texas Department of Health. I, therefore, urge the FDA to continue its study into potential harm of ingesting ephedrine and if warranted to consider exercising its regulatory authority to control the use of this supplement."

Thank you.

MR. WILSON: Thank you.

We have time for one question.

Dr. Ziment?

DR. ZIMENT: This is a rhetorical question actually. If your wife or anyone else had gone with her history of no seizures to a physician with a cold, and the physician prescribed ephedrine in some form, she might still

have had the seizures, is that correct?

MR. WILSON: Theoretically, yes. In reality, no. My wife doesn't consume products containing ephedrine or pseudo-ephedrine or that type of products. She intentionally steers away--

DR. ZIMENT: If the physician had prescribed it for a cold, she might have taken it and had the same result.

MR. WILSON: My wife is a registered nurse. She would look the drug up in the PDR and if it contained ephedrine she would not take it.

She reads the labels on cold medicine and she does not take products containing ephedrine, pseudo-ephedrine or the like.

MR. WILSON: Dr. Hsieh.

DR. HSIEH: Mr. Wilson, the question is somewhat personal so you don't have to answer if you don't feel like it. At the time your wife is taking this food supplement, was she heavy or was she thin?

MR. WILSON: She doesn't need to lose weight. Like most people that take these supplements, it's my understanding they don't need to lose a lot of weight. People are, the studies are on clinically obese people and my wife is within the height-weight target range for her.

She's not obese clinically, by no means. She's

not overweight. I'm in the health fitness industry and I can basically testify she's not overweight and she's not obese.

DR. HSIEH: So, she was thin, then?

MR. WILSON: Yes.

DR. HSIEH: Thank you.

DR. ASKEW: We will go to our morning break now. We will resume at 10:35 and we will start with Dr. Yetley giving us a wrap-up and focus.

[Recess.]

DR. ASKEW: The meeting will reconvene.

DR. ASKEW: We had a period of public comment and we have been joined at our table by Dr. David Kessler, Commissioner of the Food and Drug Administration and Dr. Larsen has a couple of administrative announcements and a clarification.

MR. WILSON: One clarification is that we do have Dr. Maury Potter, erroneously identified, a bit not totally but a bit, in the notebook. He is the assistant director for food-borne diseases. So, if you go into your notebooks and make that correction, please.

During the break, we had a little discussion. There was apparently an erroneous statement by Mr. Appler and at one point, Dr. Mike Weintraub was going to make the

correction but we're going to ask Mr. Appler to make the correction himself. And then Dr. Mike Weintraub wishes to elaborate for a minute.

Dr. Weintraub is with our Center for Drug Evaluation and Research at FDA.

MR. APPLER: Thank you, Dr. Larsen.

I want to apologize to the committee and to the audience for repeating an error that was in our report last year without looking back on it carefully enough. Briefly, there is no authorized OTC oral ingested dose for ephedrine. It only authorizes for another drug, epinephrine and I confused those two. I apologize to the committee for doing that. The oral approved dose is--

DR. ZIMENT: Wrong. Aerosol.

MR. APPLER: Did I say inhale? Excuse me, aerosol, there is no authorized dose whatever for ephedrine by aerosol in the OTC monograph and I apologize to the committee for that. I confused the epinephrine with the oral dosage form that is authorized for ephedrine. My apologies, thank you very much.

MR. WILSON: This is Dr. Weintraub.

DR. WEINTRAUB: Good morning.

I am Michael Weintraub and I am the director of the Office of Drug Evaluation V in the Center for Drug

Evaluation and Research.

The only inhaled medication made available OTC is inhaled epinephrine in the 1 percent dose and it is by the hand-held rubber bulb because we have taken off the metered dose inhalers. So, that Mr. Appler made a mistake and he acknowledged that mistake.

If anybody has any questions I would be--

DR. ZIMENT: I don't think that is correct.

I don't think you're correct. Primatene Mist and similar products are still available as aerosols.

DR. WEINTRAUB: Yes, but, well, they--

DR. ZIMENT: Over the counter.

DR. WEINTRAUB: Yes, and Primatene Mist contains ephedrine.

DR. ZIMENT: Correct.

So, it's not just a hand-bulb. It's also a metered dose inhaler product.

DR. WEINTRAUB: They are going off the market, however.

DR. ZIMENT: At present they are on the market.

DR. WEINTRAUB: Yes.

DR. ASKEW: If there are no further questions, I thank you, Dr. Weintraub.

We are going to move now into the clarification of

the charge by Dr. Yetley. I want to remind the committee members that if any of you have to leave before you think we're going to finish today--in other words, before you have a chance to give your oral expressions on the matters that I had mentioned before--we would appreciate it if you would write a summary of your comments.

Now, in this summary, you should include some response to the charge that Dr. Yetley has proposed to you, and specifically the four questions. You should indicate whether you would adopt the recommendations of the October 1995 Working Group and any concluding statements that you would care to make.

And if you do have to leave early, please come up and let Dr. Larsen or myself know and we will try and give you a chance to make it orally.

I would like to proceed now to Dr. Yetley.

DR. YETLEY: Thank you.

I hope to be brief. I will just remain at my seat. I want to go back to the paper on charging questions posed to the Food Advisory Committee. And, at the risk of overkill, I will go through these again, but I think it is extremely important that we are all clear as to what the charge and focus is.

The charge to the committee is very simple and

that is the safety of ephedrine alkaloids dietary supplements and specifically the scientific underpinnings of that safety evaluation.

Let me reiterate what I said yesterday as to what we are not about as well as what we are about. We are not about the effectiveness or the substantiation of label claims. We don't want this to be a distraction from your discussion on safety issues and, furthermore, dietary supplements can be marketed without claims, so that it is not an issue or a prerequisite for the marketing of a product.

This discussion and this decision making is not about legal standards nd requirements. We will use the scientific discussions that you have and integrate them within the legal framework with which we have to deal with but we want you to focus on the science.

This is about the scientific underpinnings to evaluate the safety questions associated with use of ephedrine alkaloids containing dietary supplements. We understand your frustrations that you don't have good data on the botanical sources that are relevant to the questions on the table. We understand your frustrations as to the lack of clinical studies on the botanical sources that are relevant to the questions on the table. We understand your

frustrations as to the lack of well-designed epidemiology studies, again, with relevance to the questions on the table.

Nonetheless, as Dr. Kessler noted yesterday, we have a public health issue before us, inaction is unacceptable. We must find a solution with the information available to us at the present time. The expertise and experience that you bring to this table are critical in helping us to address these issues.

We also understand your frustrations about how, if, should, can you generalize from drug studies and drug experiences to the questions on the table. This is a scientific call. We ask for your judgment as to the relevance of available drug data or any other data that are available to the issues on the table. We ask you to communicate what you believe are appropriate extrapolations from one context to the context that we're dealing with here.

We ask you also to indicate what cautions or caveats are needed when you make those generalizations from data collected for other reasons to the questions at hand. We emphasize the need for context relative to the dietary supplements products we're dealing with as you discuss the issues.

Unlike drugs, where you start with effectiveness questions and then deal with safety, we're asking you to start from the other end. We ask you to start with safety without consideration of claims.

We remind you that when you are dealing with botanical sources you're dealing with a family of ephedrine alkaloids not a single alkaloid as you would see in the drug products. We remind you that the market survey showed a number of relevant points.

First of all we're dealing with multi-ingredient products to a large degree. The majority of the products in our market survey had between 11 and 20 so-called active components. Others had many more. The vast majority of the products in our marketed survey already had warning labels that indicated contraindications for use.

Half of the products in our market survey had serving sizes and directions for use that would result in intakes below 17 to 20 milligrams a day or per serving. There was a diversity of products with many intended uses--weight loss, energy, body-building, street drug alternatives--but these were, to a large degree, indistinguishable. Indistinguishable in terms of the range of potencies and the amount of ephedrine alkaloids per serving; indistinguishable in their use of warning

statements.

Also, keep in mind the context of the adverse events as reported by Dr. Love. We have reviewed over 600 adverse events; we have received more than 800.

The ephedrine alkaloids containing products constituted well over half of all those adverse event reports for all dietary supplements. Half of the consumer reports, where we had actual samples of the product as used by the consumer, were associated with intakes of total alkaloids at less than 25 milligrams per day. In other words, the injury and illness that was reported was associated with an intake of less than 25 milligrams total ephedrine alkaloids per day.

Where information was available, we saw positive dechallenge, positive rechallenge and of particular concern we saw serious adverse events in the healthy adult population where such events are unexpected.

Now, let's turn again to the questions that we are posing to the committee on page three of your focus and questions. We are asking that you help us identify the issues related to safety first. And the first charge we're asking is to deal with it from the perspective of safety.

Can you identify a safe level in dietary supplements for a total ephedrine alkaloids per serving and

per day as well as ephedrine itself? And how do you think we should deal with margin of safety issues?

Can you identify questions of use for ephedrine alkaloids containing dietary supplements under which there is no risk of significant harm? And then the last question reverses the end of the spectrum that we're looking at and ask you to identify conditions of use that are associated with the risk of significant harm including the levels and frequency of use above which there is risk of significant harm.

Then if you will--I apologize for not having these in the right order--but if you will go back to page two, we have specifically listed, in the A, B, C, D, E, and it is continued on the next page, the questions or the anchor points we want you to keep in mind. A, the potentially large population that is susceptible to experiencing adverse events with the use of ephedrine alkaloids; B, the potential for additive effects of the different ephedrine alkaloids or the interactive effects to increase the likelihood of severity of an adverse event; C, other ingredients in the product with potential physiological or pharmacological activity that may interact with ephedrine or other substances to increase the likelihood or severity of an adverse event; D, natural variation of the ephedrine

alkaloids in the product; E, the fact that in the data evaluated by FDA the majority of adverse events appeared to be related to short-term use of the products, that is less than one month, and many of the events are reported to occur within the first use or on the first day of use; F, evidence of serious adverse events resulting from long-term history of use, that is the idea of chronic toxicity or chronic problems, chronic risk versus acute risk; and G, other factors that you feel may affect the likelihood or severity of adverse events or the nature and patterns of the illnesses and injuries associated with the use of these products.

Thank you.

Do you have any more questions for clarification?

[No response.]

DR. ASKEW: Thank you.

Does the committee understand what is being asked of them? If not, direct your questions to Dr. Yetley at this time.

DR. YETLEY: I apparently mis-spoke. The adverse events, half of them were associated with less than 25 milligrams per serving, not per day. So, I make that correction.

DR. ASKEW: Okay.

Dr. Fukagawa?

DR. FUKAGAWA: Could you clarify for us the Working Group recommendation in terms of dosage in that the minutes that we received suggest that there was discussion of limits between 20 milligrams of ephedrine and then 25 of the total of ephedrine alkaloids, but is this something that is, indeed, included in the recommendations? Since, if we look at the review of the charge and questions that you posed to us yesterday, nothing is stated with respect to actual milligram contents.

DR. YETLEY: We're asking a very open-ended question.

DR. FUKAGAWA: Okay.

DR. YETLEY: The Working Group--maybe Dr. Larsen should describe this better than I because he is more familiar with it and won't make a mistake.

DR. LARSEN: Well, I hope I get it right. But let me put it this way, the Working Group had on the table, at least one of the levels on the table was that which we've identified in the minutes. And, as I noted earlier, it got to be tagged the Tyler-Croom proposal.

The Working Group also did discuss and there were other levels discussed, several levels below that were mentioned at times and I believe at least one member might

have suggested a level above that. But that seemed to be the starting point that at least a number of the Working Group members were working from. And as I said, there were other levels suggested that were below that, as well.

DR. ASKEW: Dr. Hsieh and then Dr. Guzewich.

DR. HSIEH: If ma huang is not to be recommended as to be for supplement, will that mean that it cannot be sold in the market at all as a medicinal herb?

DR. YETLEY: I can only speak on the part of the dietary supplements and that's really what you're dealing with here. You're really dealing with the context of dietary supplements.

DR. HSIEH: Right. If ma huang cannot be sold as a dietary supplement, then it cannot be sold as a medicinal herb, is that correct?

MR. SCHULTZ: There are other statutory routes to getting products on the market, obviously, other than dietary supplements. One possibility would be it could be sold as an over-the-counter drug but those are different standards than the standards you are looking at here.

DR. ASKEW: Mr. Guzewich?

MR. GUZEWICH: Yes, just a response to Dr. Fukagawa there.

Because I heard this said repeatedly the last day

and a half and I got kind of tired of hearing it. From the minutes and I was also in attendance at the meeting and I just want to read part of that section because I think it was misquoted repeatedly here the last day and a half.

It says here about this idea of the quantity of the concentration that is in everybody's notebook. One suggested proposal was per unit limitation of 20 milligrams of ephedrine, 25 milligram total of ephedrine. That was one suggestion.

However, a wide range of lower levels were also discussed and then the sentence, "The group suggested that FDA begin its consideration at some level below that currently used in OTC drugs."

So, it keeps being characterized as the group recommending 25 milligrams but I recall it and that's not the way the minutes reflect it either.

DR. ASKEW: Yes, I think you are absolutely right. Committee members, the full minutes are in Tab D of your notebook if you want to refer to it. It is my understanding that an exact dose level was not arrived at, nor will an exact dose level be arrived at by this group here. You're simply going to give your opinion as to what you might consider, if you can venture that, a safe dose. The FDA will take that information into consideration.

So, when you indicate whether or not you approve the Working Group minutes, this doesn't mean that you approve 20 milligrams or 25 milligrams or a specific level. You basically approve the report and what we have added to that will also go to the FDA for their information and action.

Further questions or clarification?

Yes, Dr. Hui.

DR. HUI: I want to follow-up with Dr. Hsieh's question. In California, a lot of the licensed acupuncturists have been extensively instructed on the use of herbs. And I just want to, you know, find out how this action may affect the availability of products that would include ephedra because they are very concerned that both as raw herbs or also as compound formulas that has been used traditionally for thousands of years in the management of patients with respiratory disorders.

DR. YETLEY: I'm wondering if somebody from OTC Drugs could answer that question.

DR. WEINTRAUB: I did not hear the question.

MR. SCHULTZ: Let me just try. I don't think that there is really any more to say than what was said. And that is, if the substance doesn't qualify under the standards for dietary supplements, and that would be a

decision that the agency would make after this committee made a recommendation, but the scientific recommendations here, we didn't have to feed into the statutory standard.

But if it doesn't, then there would still be the issue as to whether it could be on the market as an over-the-counter and that takes into account different factors including the benefit and efficacy of the product.

But that would be a whole different consideration but that avenue would certainly be open.

DR. HUI: So, you mean that ma huang would be taken off from all the pharmacists in Chinatowns and also ephedra will be taken off from the plants, manufacturing plants of herbal companies?

MR. SCHULTZ: No, not necessarily. Over-the-counter drugs can be on the market several different ways. But it doesn't always require pre-market review and the agency would have to, in implementing some sort of decision, take into account the existing market and how to phase something in or phase it out.

DR. ASKEW: Dr. Weintraub, did you get the sense of Dr. Hui's question and Mr. Schultz' response. Did you care to add to that?

DR. WEINTRAUB: Well, just that Mr. Schultz is, of course, correct. There are a number of ways. The monograph

could be amended, because it is a final monograph, now it can be amended. The drugs can undergo the NDA process. There are many, many routes for keeping the herbs on the market as over-the-counter drugs.

DR. LOVE: Could I just comment, too? That from the perspective of ma huang from an Asian practitioner, they are using it as a medicinal and it's not purchased for commercial use or distribution. And they are not labeled as dietary supplements and so how the agency views them would be different than these products that we are considering as dietary supplements. And I think people need to remember that.

DR. ASKEW: Yes. Just remember in this discussion to identify yourselves. I think we have kind of moved past the points of clarification and entering into general discussion. That is fine because that is what we were going to move into next.

So, we will have a period of general discussion and then we will then move in, probably after lunch, to our specific consideration of the FDA charges.

Raise your hand and I will recognize you but identify yourself. I saw Dr. Ziment first.

DR. ZIMENT: Yes. I am concerned about what our duty is to the public and what the psychological impact of

what we might advise here in terms of how the news media will react to it.

If we say ma huang and ephedra products in dietary supplements are unacceptable, does this create the concept that people who want to take these drugs have to buy orthodox ephedrine over-the-counter or would it give the message that we think people should go to MDs and have them evaluate the patient and then prescribe the ephedra products?

DR. ASKEW: Dr. Kessler?

DR. KESSLER: I think you need to look at the questions Dr. Yetley has charged this committee, because I do see some of the discussion as straying from those questions. I was just advised that you focus on those questions and that's really the job today. It's not views of a product. The questions are questions about safe levels, adverse reaction occurrences, that's what we need help with. It's not about the use of medicinal products and the regulatory status.

If you could focus we would appreciate that very much.

DR. ASKEW: Dr. Blackburn and then Dr. Croom and then Dr. Georgitis.

DR. BLACKBURN: I withdraw my question which had

to do with things Dr. Kessler just mentioned.

DR. ASKEW: All right, then, we will move on to Dr. Croom.

DR. CROOM: Let me add a little information on the dosing and things since I've been particularly mentioned in some of the discussion last time including levels. One of the things that we discussed in the committee was certainly that when you set the level at 25 total ephedrine alkaloids, but ephedrine being seen as the most cardio-active and potentially the largest side effect being lower at 20, was one of the things that was discussed.

I want to also point out, however, that there was also consensus certainly between Dr. Tyler and I and this was also forwarded to the chairman, that if things were used in combination with things like caffeine that we were both in agreement that ratio--this is individual dose--should be a 10/15 level, not a 20/25, because of what was unknown we felt like in the lack of data, even though there is some data.

I also want to clarify another thing because we get to this on the dose I think when we look at material time and extent. If you take the Chinese pharmacopeia the range of ma huang or ephedra that you can use is 1.5 to 9 grams. Actually most of the formulas used by practitioners

that I've seen range around 6 grams but there is a ma huang tong that is based on a 9-gram dose.

If you take the more moderate, 5-to-6 grams, and you say the Japanese pharmacopeia is the only official source that sets a minimum, which is .6 percent, if you take in commerce, no matter what these range of values you've seen, the average is probably 1.2 percent. Then you will find that if you took 5 grams, which is approximately two table spoons--I have cut it and weighed it myself--that you will find that at a .6 to a 1.2 that you are getting 15 to 30 milligrams per table spoon in ma huang tea for the minimum concentration of .6 to an average of 1.2.

If you take the two table spoons, therefore, you are at the same dose that we found most physicians using, between 25 and 50 for the pure compounds.

Because of unknown factors that we can all see in this use, certainly Dr. Tyler and I are in agreement, that we should look at lower doses of the 10-to-15 is what I also want to mention here for the different combinations and things that have not been used for such a material time and extent.

And so, where I'm trying to lead us is to the question to say in my opinion we start asking what is the material time and extent we've heard if we take it on today

to whether it is Canada and the doses we heard for ma huang at 6-to-8 milligrams, whether we see that there are within the Chinese tradition or within our physicians' experience whether it is pseudophed or ephedrine--ephedrine being definitely the one that causes the most sever effects--to look for some guidance in setting whatever levels we see are going to be safe.

I want to end up my comment here to say that I'm used to setting monographs and I even teach a course to our graduate students in pharmacognosy on botanical monographs. I think it is important that we not only taught those but the very good questions we were giving to say, overall, you do have to be guided by how it's being marketed, what's the potential misuse to set the final levels.

I think we have to have an overall comprehensive thing to say what we shouldn't do and I will leave the other comments until later. But I thought that would give us a transition, hopefully, into our charge and focus.

DR. ASKEW: Thank you, Dr. Croom, I think that was helpful in explaining how you and Dr. Tyler arrived at the general ballpark figures that you did.

We will move on to Dr. Georgitis, you have a comment?

DR. GEORGITIS: Dr. Love, I have a question for

you, in terms of the serious adverse events, below the median value of 20 milligrams per serving of the ephedrine alkaloids, do you have a percentage as to how many of those out of the total adverse events?

DR. LOVE: We haven't expressed our data in that form because, of course, we have only a relatively few samples where we've been able to collect the sample that the consumer was using at the time of the injury and be able to analyze that.

But, clearly, they are below in a certain number of cases of very serious adverse events which appear to be temporarily related including a couple of the ones I showed yesterday where the levels are below the median.

DR. ASKEW: Dr. Kessler?

DR. KESSLER: Could I just follow-up on that? If you look at the median, what about 20 depending on whether it was label or consumer use?

DR. LOVE: Right, 20 to 25 depending.

DR. KESSLER: And 50 percent of the adverse reactions were greater or 50 percent was less. If you look at the universe of significant adverse reactions, just narrow it, I mean as the question just did, to deaths or heart attacks or strokes or psychosis--things that everyone would agree would be significant adverse reactions--and then

you asked for relatively clean cases that didn't have a lot of confounding factors--where you have a medical examiner, where you have a sample--could you just go through those cases and at what levels you saw significant adverse reactions?

DR. LOVE: Well, unfortunately, I don't have all the data in hand here, but there are a number including very recent cases for which we yet don't have all information on how the consumer used the product but a more recent death, again, it appears to be a cardio-myopathy case. The total alkaloids in that case are 10 milligrams, total alkaloid. As I stated a death from what appears to be long-term use of a product containing 10 milligrams of total ephedrine alkaloids.

DR. KESSLER: That was per serving?

DR. LOVE: Per serving, yes, sir.

DR. KESSLER: And just go through that case. I mean just so we have some--I mean the best data that we have.

DR. LOVE: Well, as I stated I don't have all those details.

DR. KESSLER: I'm sorry.

DR. LOVE: I don't have all those details in hand. We do have certainly myocardial infarction is one of the

cases I used as an illustrative case. That the total alkaloids was in the 20 milligram range. And ephedrine was in three to five range. There are other cases where seizures appear to be in the 10-to-15 milligram range of total ephedrine alkaloids often on very short-term use.

So, it is certainly within the range. I point out that the mean in these products is very broad. And the median is really what we're looking at. And as Dr. Kessler indicated, as the consumers use them and sometimes they may have used more or less, it was approximately 25 milligrams of total ephedrine alkaloids. On a milligram per serving basis this was 20 milligrams and we have more samples to analyze. So, 50 percent of all the samples that we looked at fell well below that level.

DR. ASKEW: Dr. Marangell has a question.

DR. MARANGELL: Dr. Love, as a follow-up, you had mentioned yesterday that there were serious adverse events in the 1-to-5 milligram range. Could you clarify for us what types of adverse events and also as a follow-up, would you clarify the autopsy report that's been questioned by some of the public speakers?

DR. LOVE: When I was talking about that I was talking about total ephedrine alkaloids and I mean, total ephedrine and we have myocardial infarcts in people with

normal coronary arteries. We have seizures. We have changes in liver function tests. We have deaths at that rate.

DR. MARANGELL: At 1-to-5 milligrams--

DR. LOVE: Of ephedrine.

DR. MARANGELL: Thank you.

DR. ASKEW: Clarification of the autopsy.

DR. LOVE: The clarification of the autopsy report is that information on the consumer's negative ethanol and cannabis levels are in the record.

DR. ASKEW: Thank you.

Dr. Bruner?

DR. BRUNER: That was my question.

DR. ASKEW: Dr. Ricaurte?

DR. RICAURTE: This is a question addressed either to Dr. Love or perhaps Dr. Weintraub. What I'm puzzled by is the apparent disconnect between the data on the products we've been discussing the last day and a half and what several members of the committee has said is our 50-year long experience with OTC, ephedrine-containing products.

Why the apparent disconnect? I say, apparent, because the issues of some of the adverse effects, certainly they haven't loomed as major concerns with OTC products contained in the ephedra alkaloids. Is it the reporting

system? There is a disconnect there that I would like to try to understand. And the reason I ask the question is because if we are going to use, as was suggested by the Special Working Group before, as a benchmark or a starting point on dosage issues, prior experience with OTC products containing the ephedra alkaloids, then I think the issue of why the apparent disconnect exists is critical.

DR. LOVE: Of course, the reporting systems are different and the products are very different. And what we've tried to do is take all data that are available and unfortunately most of the scientific data that is available on any of the ephedrine alkaloids are because of products that are used as drugs and are very defined chemicals.

What we see in these botanicals is we have a mixed alkaloid pattern. And, as Dr. Yetley indicated, there are many other ingredients that are in them. Now, both foods and drugs use passive surveillance system. Drugs also has more active systems where they can get at the situation of incidents in prevalence data that we don't have. And since they have a defined product they can do that, in part, from marketing data.

We do not have defined products here. The product from one manufacturer containing ephedrine plus these other ingredients cannot be compared necessarily to a product from

another manufacturer that may be listed as containing the same ingredients. You don't know what their source is, you don't know what their potency or anything else is. And because there can be natural variations, even the products from a single manufacturer can have lot-to-lot and batch-to-batch variability that may well affect their safety profile.

So, it's a very different situation than what we see in drugs.

DR. HUI: Can I add to that answer? Having worked with patients with asthma and heart failure and I've used antagonists. I mean there is an increase in deaths in patients using, you know, agonists. There is some concern using those agents that stimulate the heart and also there is increasing incidence of asthma deaths. That is why whether the agonists are involved under a lot of debate. And remember when you use ephedrine for asthma conditions if the patient respond to it they stop. If they didn't respond then they will probably go to see a doctor and they will be under medical supervision.

Now, if they die, it probably will be thought as related to their asthma. So, we cannot really compare, you know, the two groups. Because asthmatics already have enhanced echeneric drive and a lot of these patients may be used to that and whereas a lot of these other patients they

are not used to sympathetic stimulation and while they use it to enhance performance, exercise, they may be under a lot of stress and they may also be having a normal risk factors for any of these other conditions.

So, I think that that may be part of the reason why the risk is because in addition to pharmacokinetics variability given to ultra levels, there is also a pharmaco-dynamic variability.

DR. ASKEW: I'm going to go to Dr. Inchiosa and then Dr. Ziment and Dr. Chassy.

DR. INCHIOSA: Since this is a period of general discussion, I would like to return to a philosophical issue that has been mentioned by a number of speakers and that is the context in which the drugs are being used. Dr. Ziment also brought this up when he asked Mr. Wilson, do you think if your wife had taken an over-the-counter preparation of ephedrine would she have had the seizure? And she probably would have had the seizure, but I think there it would have been in the context that she would have been taking that drug presumably for asthma and there was an indication.

And when one has an indication, then one accepts a certain amount of risk. And so when we are even talking about safe levels, there is never really a completely safe level. It's always a safe level in the context of the

benefit.

And so I think this is a crucial situation that we are going to have to deal with when one begins to talk about any safe level where there is no indication or clear therapeutic indication. And our whole pharmacopeia structure is based on indications. Drug manufacturers can only label what the FDA says they are indicated for but then we have the wonderful medical, clinical situation which develops many accepted indications. They are not labeled even as being but they are known by the medical community as being accepted. They are published by the USP as accepted indications but it's all based on that structure. We use active principles for accepted or approved indications, then tolerating a certain risk.

And I think that is the problem. And I was glad to hear some of the discussion about the routes which might be used to have these perhaps legitimate herbal remedies transferred to an over-the-counter structure which defines an indication in that context and a dose which is going to accept some adverse effects.

DR. ASKEW: Dr. Ziment?

DR. ZIMENT: I want to follow-up what Dr. Ricaurte was referring to. I still don't feel that I understand what the reported and recognized dangers are of taking either

over-the-counter ephedrine or even pseudoephedrine or phenylpropanolamine. And I certainly have prescribed agents of this nature. And I feel there is a disconnect in that we are hearing a lot about the dangers of ma huang and ephedrine without knowing the dangers of comparable orthodox drugs.

A second comment which maybe we will have to think about later is should we gather, as a result of our thinking in regard to ma huang, that ephedrine as a prescription drug should be considered as an adjunct to a dietary regimen or for helping athletes gain energy? And would it be legitimate for doctors to prescribe these drugs for those purposes?

DR. ASKEW: Is that a philosophical question or are we bearing in on what we are supposed to be considering here?

DR. ZIMENT: Well, Dr. Love, perhaps can give us a little bit more information on the side effects that are actually recorded, even on a year-to-year basis in adverse drug reports on the legitimate ephedrine products.

DR. LOVE: I don't have that data and I will defer to people from Drugs on that. But I would like to comment on the clinical trials that have been published in the scientific literature as well as some of those that are

proposed in the area of weight loss.

And the overwhelming majority of these are efficacy studies where some information on potential side effects may have been provided. These are not studies that are designed and are powered and are conducted to evaluate the safety of any of these botanical type products.

So, using those other kind of data to support the safe use of a botanical is not a legitimate use of this data and will not help.

DR. ASKEW: Dr. Weintraub, do you wish to comment?

DR. WEINTRAUB: Yes, if I can help. Over the past few weeks, we've been looking at the ephedrine adverse effects. And the first thing I can say is that there are no serious adverse effects within the dose range that is printed on the label. There are some adverse effects that occur due to taking of products with different names which may mislead the public or be sort of fanciful names that would indicate a different indication other than bronchial dilation.

So, but, as bronchial dilator, used as a bronchodilator there are no major adverse effects.

DR. ASKEW: Dr. Chassy was next.

DR. CHASSY: I'm still interested in incidents and prevalence. And I don't know if these numbers are available

but I would be curious to know how often one sees a seizure, a spontaneous seizure or a myocardial infarct in an otherwise normal person without any underlying etiology that is evident. Are those kinds of numbers available?

Does it happen, in fact?

DR. ASKEW: Would anyone care to respond to that question?

DR. HUI: I can't give you off-hand what the data is but I'm sure that there are data available.

DR. JASINSKI: There is a whole literature on people suddenly dying from apparently cardiac deaths without any unexplained phenomena. I mean there are people who talk about the sudden death syndromes and it has been publicized no this. And there is a literature on this if somebody wants to look it up.

Also, with seizures. I mean it is not an uncommon thing for people to--I live in an institution where people show up in the emergency room having a seizure and right now if they have a seizure they are a drug-abuse or probably until otherwise proven in terms of doing this.

So, it's not an unusual thing for people to show up in an emergency room with a seizure.

DR. ASKEW: Dr. Ricaurte, do you want to respond to that or another question?

DR. RICAURTE: Well, with the issue of seizure disorder and the particular case of Mr. Wilson's wife. I happened to be talking to him before today's meeting but a very, I think, essential feature of that case is, that was left out or perhaps not sufficiently emphasized, is that she is a nurse. She is aware that she is highly sensitive to any ephedrine containing product. Indeed, she actively avoids such products. She gets into trouble because she is not an informed consumer.

Had she taken--and I think the point was made earlier--had she taken an ephedrine containing over-the-counter product, the consequence might well have been the same.

DR. ASKEW: Thank you.

Apparently, it occurs, Dr. Chassy, or do you want to go with it from there?

DR. CHASSY: I just wanted to make the point that if millions of people are taking products that contain ephedra alkaloids and we are seeing a very low incidence of these kinds of serious effects, we need to know whether that incidence is any greater than spontaneously occurs.

DR. ASKEW: And I don't think that we can give you an answer to that.

Mr. Israelson wanted to comment next.

MR. ISRAELSON: I had several questions for Dr. Love. First, on the formulas, which cause these serious adverse reactions at low dosage, 1-to-5 milligrams, do you have the formulas, themselves, so we could identify what else is in there? Because I'm not sure we have that data and we would very much like to know what it is.

DR. LOVE: I do not have that in hand and we actually were just analyzing that data over the weekend. It's very new data even to us.

MR. ISRAELSON: Okay. We find that to be very significant in terms of what really would have happen particularly on the ingredient listings, together with an actual analysis of the material itself, so that there aren't compounding factors that haven't been identified.

DR. LOVE: And as we finalize results, we, of course, intend to put all that in the public domain.

MR. ISRAELSON: Thank you.

Very quickly, a couple of other things. How did you determine the actual dosage of these specific cases? Was it based on the label recommendation or interview with the patient?

DR. LOVE: We had both information. The information that I was presenting as the consumer used it were in cases where we specifically had information by

interview on how the consumer used the product, how many tablets, when, et cetera, as well as usually label and labeling information that indicated what the directions for use were.

MR. ISRAELSON: Okay. One of our concerns is that if someone has taken too much that they can be reluctant to tell you that for obvious reasons. What is your confidence level that you have data from those interviews that is reliable?

DR. LOVE: Are you asking if we can verify that or any other information that our patients give us? I mean that's a very difficult question. If the patient told you that they took an over-the-counter product at X value, you would believe them.

MR. ISRAELSON: We think it's important to the basic issue whether or not--because it has been suggested that people have been abusing these products, and if that is the case then that becomes a relevant and important factor.

DR. LOVE: That is true but most of the information that we have indicates that they are using them within the directions of use as indicated on the label and labeling and are not abusing these products.

DR. ASKEW: Dr. Kessler?

DR. KESSLER: In the Tufts case, the 24-year old,

the level there, there was no blood plasma level. There was some that was found in the urine that would suggest a relatively low level.

DR. LOVE: It was a relatively low level but, of course, we did not know the interval between the last time he used the product and when his urine was analyzed which, of course, would affect the level because of half-life issues.

DR. ASKEW: Dr. Jasinski?

DR. JASINSKI: I just think there is a body of information which has not been particularly discussed and which I have alluded to. And I just tell you my particular perspective on this. From 1965 to 1985 I was at the Addiction Research Center and I had the responsibility of the human research and the human abuse potential studies. In 1976, I became director and at that time, in 1970 after the passage of the Comprehensive Drug Abuse Treatment and Prevention Act, which brought the amphetamines under control, basically through an Act of Congress, we had the responsibility for doing the abuse potential studies and looking at this.

It was mandated to us and this was a joint activity between NIDA and the FDA. In this, we did consider the abuse potential of ephedrine. And did learn a lot about

the human pharmacology of ephedrine and the toxicity of ephedrine. The basic issue is that ephedrine is a typical amphetamine-like drug. It looks just like amphetamine.

If you give it the difference is in a milligram-for-milligram potency. To get an effect at 10 milligrams of amphetamine you have to have 50 milligrams of ephedrine, either orally or by injection. That is ephedrine-like amphetamine does not have a first-pass metabolism. It's almost completely absorbed.

The second issue is that this puts it identical to benzoin-phetamine. On a pharmacological basis, the argument could be made to bring fentramine under the Controlled Substances Act with the amphetamines as the same level of benzphetamine.

In the 1970s, I appeared before the Senate on behalf of the FDA defending their scheduling recommendations and in this did look at this issue. The differentiation from ephedrine from the other amphetamines were for two reasons. Even though they pharmacologically were equivalent, the issue which was here was that at that time there was a long history of ephedrine being sold as an over-the-counter primarily for allergy and asthma.

Secondly, the major public health and social

problems with the amphetamines were not from the oral preparations but were diversion into the intravenous route. There were just very much like this and an occasional death that was occurring from the amphetamines questionably related to the cardiac effects. Most of the deaths and the public health problems related to the people shooting up intravenously and getting infections.

There is another set of experiences which I think is germane to this. And that is in 1976 I did get a call from my then boss, the Director of the National Institute on Drug Abuse, with regard to cigarettes and tobacco which was an herb and which was exempted by Congress from consideration because it was considered a substance for the purpose of this.

And I took the position and instituted a series of studies which basically was that this contained an alkaloid which was nicotine. And we did the abuse potential. We gave it intravenously to people to addicts and showed it produced effects like cocaine and amphetamine, we did human self-administration, we did a whole psycho-pharmacology, and demonstrating that it had an abuse potential. And then subsequently with the courage of my then, chief, the head of the National Drug Abuse, Bill Pollin, went to Congress and got them to say that it was addicting. This had great

implications.

Now, in the considerations, what strikes me in here that this is germane to these issues. The issue was that we viewed nicotine and we viewed the cigarette as a delivery system or a carrier for the nicotine. And in this, it raised the same issues, I think that George raised, nicotine, itself, is a reinforcing drug, has a toxicity.

It does not explain all the toxicity of the cigarettes. Nicotine is not a carcinogen by anybody's definition. Nor probably does it account for the cardiac deaths that are associated with this. It is some other constituency. If you look at cigarettes and you look at analyzers there are 4-to-5,000 chemicals which exist in a cigarette when you burn it into smoke. There is no way in God's earth anybody has got enough money to identify and do toxicology on all of these particular compounds.

So, you had to make the decision in this way. If you look at the ma huang in these various preparations, if I understand Dr. Love, is that if you consider this a delivery system for ephedrine you know the toxicity of ephedrine, it is not particularly toxic in my estimation. However, no matter what preparation you make the safety of the preparation is going to be less than the pharmaceutical.

We are reversing this. I mean I come from a

particular background of trying to find safer drugs and we have had a history in Western medicine of taking drugs out of Oriental medicine or out of folk medicine, isolating the active ingredient and making it pure. We are going backwards.

Inherently it's going to be unsafer, not as safe because of the variability of the preparation. Nobody knows where the plant comes from. Nobody knows from the start what is added to the plant. Nobody knows what the constituencies are. I also get very concerned because I do not think that coding a long history of use in Oriental medicine is going to focus on the safety at the current time. We have no idea of whether the plants are produced in the same way, whether they are grown in the same way, whether pesticides are added, whether they are grown in places where there is an industrial toxic waste. Who knows in terms of doing it?

I also, that's my bias I think in this. I have a question for Dr. Love.

The death issues, one of the things which I was looking for is that HHS has another system which is the DAWN system. And one of the issues would be--there is always debates on deaths, you know, in drug-related and drug-associated deaths--has this shown up in the medical examiner

data which is generated by HHS in the DAWN system?

DR. LOVE: I don't believe it has shown up yet. But one of the problems was that they didn't have a way of classifying these particular botanical products and that was the same for the poison control data. So, if you looked for ephedra you would not find it because it was classified under a miscellaneous category where you had to search entire records to find the relevant information.

Now, I do believe that DAWN and these other systems, including those from poison control are now aware of the problems with certain of the botanicals and have made attempts to address this so that in future data we will be able to see this.

DR. JASINSKI: Just looking at this, I have heard a lot and I try to give my impressions. There has been a great increase in the number of these products and the sale of these products since 1994, is that after the passage of this law that there has been an increase in the sales of these products?

DR. LOVE: I believe that industry can address that better but from the perspective of these products if you consider them in the context of weight loss, much of that is driven by what has been published from the clinical trials from Denmark using combinations of pharmaceutical

grade ephedrine with caffeine. And many of these trials are in the late '80s and early '90s.

DR. JASINSKI: No, no. You had this table of products and most of these appeared since the passage of this law classifying this as a herb? Has there been a sudden increase?

DR. ASKEW: Dr. Jasinski, I think that Mr. Israelson can probably answer your question.

MR. ISRAELSON: Yes. The DSHEA is not the predicate on which these products are being sold today. Many of them were on the market previous to October of 1994, as early as early 1992.

Certain different variations on those themes and perhaps the total number has increased. I would think that is true, but the law, itself, is not the reason these products are now on the market.

DR. JASINSKI: I'm not looking for causality. The question I was asking Dr. Love was she made the point today that showed up in the DAWN system. The DAWN system is always two to three years behind because the government never really enforces its contract.

DR. LOVE: Correct.

DR. JASINSKI: So, they are just publishing the 1993 or 1994 data now I think.

DR. LOVE: That's true.

DR. JASINSKI: So, if this was starting at 1993 and you always have a lag between the sales increasing and the particular reports. So, but you have been looking through the DAWN data, have you gone specifically to ask them to look for these products?

DR. LOVE: We have made attempts to contact them and to see what some of the information is in their system. And as I said, part of it is a classification problem and part of it is, as you state, they are looking at data that is one to two years old.

And I think from the information that Mr. Israelson and others can give, is that the market share of these type of products is probably increasing and it's probably true also that we didn't see a lot of them before about 1992.

So, you wouldn't have expected to see a lot of adverse events coming into any kind of system before then/

DR. KESSLER: Dr. Jasinski, we have some other people that want to ask questions, are you satisfied?

DR. JASINSKI: Yes, I've gotten my answer.

DR. ASKEW: Okay.

Dr. Harlander?

DR. HARLANDER: No, I'm fine.

DR. ASKEW: Dr. Georgitis has to leave at 12, so, we will get his summary statement right before we break for lunch.

Dr. Woosley.

DR. WOOSLEY: I wanted to address the disconnect that was discussed earlier between the experience with the OTC product and these reports that Dr. Love has summarized.

I don't think there is a disconnect for me at all and I think Dr. Love addressed that in the formulations issue and Dr. Jasinski addressed it in his comments.

I would only point out that I don't think that Dr. Weintraub meant to imply that there weren't adverse reactions to the OTC product. I think he was saying that there are no reports in the data base but that is not a surprise either for two reasons.

One, people who take OTC products for medical reasons will read the label and exclude themselves if they have predisposing factors. I think they will be more likely to take the product for its intended use and in the intended manner which is quite different from the use that we have heard about where people are taking these products, the food additives, dietary supplements for other purposes for more prolonged periods of time and in doses quite higher than recommended.

So, I would also say that even though there are no reports in the literature currently for the OTC products, it has been long known, as we heard about from the Chinese medicine, that ma huang and ephedrine can cause death, heart attacks, stroke, and all of these reactions that are in this data base. So, to me, there is no disconnect.

DR. ASKEW: Yes, Dr. Guzewich.

MR. GUZEWICH: We have several physicians at the table here who have had a lot of experience. I just wondered if any of them have ever treated any patients who have had any of these effects?

DR. ASKEW: Well, we have some information here. Let's go to Dr. Ziment first.

DR. ZIMENT: I think one of the great paradoxes that I'm faced with is that having used ephedrine in the past, as far as I'm concerned, as a physician who treats a lot of asthma and upper respiratory infections, I wouldn't have minded if this drug had been regarded as obsolescent and removed from the formulary because there are superior drugs. And it's really curious that an interest in ephedrine is now being raised because of the introduction of ma huang into Western medicine, not really for the treatment of asthma, but for the treatment of other purposes.

However, although I say ephedrine was relatively

obsolescent, that is simply because it's not a very good drug for asthma. There are far better drugs which are more convenient to give, and yet at the same time I don't think there has been a large volume of literature, and certainly my own experience supports this, to judge ephedrine as being a dangerous agent. It had a lot of side effects when used in the orthodox fashion. It caused nervousness, anxiety, palpitations and insomnia.

I don't recollect many cases ever reported of seizures, unless they were coincidental, and of heart attacks, unless it was in a person who was liable to have a heart attack because of other conditions. So I would say my own experience of ephedrine is that it was a relatively safe drug, but is a relatively third-rate drug.

DR. ASKEW: Now, we'd like comments bearing directly on if you're a physician, if you've had some experience with adverse reactions.

Dr. Ricaurte, did you have a comment there?

DR. RICAURTE: The direct answer to your question is yes. We've certainly seen neurologic complications--specifically, vasculitis, as well as seizures--in association with the use of pharmaceutical-grade ephedrine. I don't think those cases are particularly unusual to the practicing clinician.

I wanted to get back to Dr. Woosley's point. I tried to emphasize the apparent disconnect. I don't think you and I disagree. Yesterday, you made the comment that you weren't particularly surprised at what we are witnessing over the last year or two, given what you know about the pharmacology of phenethylamines, including ephedrine, and you suddenly start what I'll term as indiscriminate--with indiscriminate distribution of these compounds.

I think your point yesterday was that you're going to have a fraction of people--I don't know exactly what size, but that are going to develop complications and that didn't particularly surprise you, and that some of those complications can be serious. That doesn't surprise me either.

The issue of apparent disconnect becomes, then, because I don't see Dr. Kessler organizing a meeting to address ephedrine OTC and convening an advisory group seeking advice as to what to do with regard to the safety of these compounds, and yet here we are. So what this issue, I think, dovetails with is something that has come up before, and that is that we're getting information on a numerator which, based on what you've said about the pharmacology of other amphetamines and based on experience with other amphetamines, we know that that numerator for these

compounds--regardless of which one was put out on the market in the way that the ephedra alkaloids have, I don't think it would surprise any of the physicians familiar with the compounds that you're going to have a small number of people getting into trouble.

Now, the issue then is what is the denominator for--I mean, that's the only way I can try to get at that issue of safety as the agency seeks advice. So it just--I'm just puzzled and I'm not sure that I still understand why the particular concern.

DR. ASKEW: Dr. Kessler would like to respond to that. There are a number of other people who would like to respond. We're going to--we'll let Dr. Kessler respond and then we're going to go to the two people who have to leave early. We can consider the rest of the discussion after that.

Dr. Kessler?

DR. KESSLER: Let me repeat what I said yesterday. I was informed and I looked into with my colleagues two deaths of individuals in their early 20s, healthy, that medical examiners believed were associated with the use of these dietary supplements. I was not brought two deaths--ever brought two deaths of healthy 20-year-olds taking the product for asthma. That's why I have asked this committee

to refocus in a little more exact way since last October.

Is that helpful?

DR. RICAURTE: Yes. I guess the point I would make is even in my brief time as a neurologist, I can point to cases in the literature, as well as personal experience, where young adults using ephedrine have developed vasculitides, infection of the blood vessels or the brain, that terminated in death. They are serious. They obviously warrant attention, and my point is that if we're going to focus on the ephedra alkaloids, I guess the issue--we're seen this before, we're seeing it now, and it's not that I would downplay the concern, but it takes me back to is it the preparation, is it the purity, is it something about the product, or is it truly the ephedrine.

DR. KESSLER: All those are very legitimate questions about the products that these two individuals have taken. One was clearly masqueraded as a dietary supplement, but was being sold as a street drug, I mean, to get high. The other was used for building body mass in somebody who wanted to use it, I mean, as a weightlifting kind of supplement.

Let me just add one point that may be helpful in your discussions because we do ask are there safe levels. Certainly, the information about the compound and the

toxicity of the compound in a variety of contexts is important, and that data is important and is certainly appropriate for you to look at and ask Dr. Weintraub what that database is. But in the end, the question about safety that we're asking you today is safety in the context of a supplement to the diet. That's what we are asking you for. We are not asking you for safety in the context of an asthmatic.

DR. ASKEW: Thank you for those comments. Dr. Georgitis has to leave and he's going to serve as a model for our first summary stater. We ask him to give his views with regard to whether or not he accepts the working group committee's report, and also the charges that have been posed to the Food Committee, and then any other comments he wants to make. Then we'll go to Dr. Clydesdale.

DR. GEORGITIS: So I'm the lead-off hitter? Having heard for the last two days the specific information that has been addressed, I think the working group recommendations are clearly well-defined. I have no problems with accepting them as they're written. My concerns have been the lack of scientific data on this product as it is recommended as a dietary supplement.

A lot of the confusion arises with the fact that there is an over-the-counter medication, which is ephedrine

hydrochloride. We unfortunately, being in science, need specific data. The adverse events clearly are related and can be attributed to the pharmacological activity of ephedrine, and far more disturbing is the abuse potential of this product.

Because of that, and because of the information that has been provided us by the Chinese about their indications of the product and the fact that there clearly is even adverse events at low doses of the ephedrine alkaloids with, unfortunately, death associated to this--and even more so the lack of standardization of the product that we as Americans should expect and the variability in lots obtained of a product that's out there are very disturbing to me as a physician.

I would recommend that we follow the guidelines as recommended by the Canadians, the state of Texas and the State of Ohio and we remove ma huang or ephedrine alkaloids as a dietary supplement.

Thank you.

DR. ASKEW: Dr. Kessler?

DR. KESSLER: Would it be possible for you to just quickly go through the questions and try to answer them, in addition to the important comments that you've made? I'm not diminishing, but for the record it would be helpful if

you would just go through to the extent you can.

DR. GEORGITIS: Okay, I'll try.

DR. KESSLER: Thank you. I appreciate it.

DR. GEORGITIS: This is very difficult. To identify a safe level, I obviously cannot identify one. There's no scientific data which shows that 1 milligram is any better than 5, which is any better than 10, which is any better than 30, and that goes both for the ephedrine alkaloids and for ephedrine itself. Therefore, question 2 is sort of superfluous. Since I cannot identify a minimum safe level, I can't give you a range either.

It is clear to me that question 4 could probably be answered easier than question 3 in the fact that people that use it and abuse it are at risk. People who have a preponderance or a reactivity to ephedrine compounds may be at risk. Obviously, children are clearly at risk for overdosing and having toxic reactions, which is very bothersome to me as a pediatrician.

Therefore, I mean as a dietary supplement, I can't really answer anything in terms of no significant harm. I think that I can't identify a safe range. Therefore, I can't give you anything where there's no harm for question number 3.

DR. ASKEW: Thank you, Dr. Georgitis. Dr.

Clydesdale also has to leave early and he would like to give his statement. Dr. Clydesdale, we would also like you to specifically attempt to answer the questions.

DR. CLYDESDALE: Thank you. I'll try to answer them in order, and thanks for leading off. I don't agree with the recommendations of the working group, which I believe were made without all the evidence that was available at this meeting because I don't think they went far enough.

In answer to the questions, the charge that was given to us, like Dr. Georgitis, I'm unable to identify a safe level with the evidence available for a product that is sold as a supplement and not as a drug. This conclusion was reached after reviewing what I considered compelling data on adverse effects. Although a cause-effect relationship was not established, there was a common thread throughout all the studies, which was the presence of ephedrine or ephedra herb. The adverse effects data, however, were not considered in isolation and my conclusions were not based solely on adverse effects.

I have great concern for the lack of purity in botanicals as compared to drugs, and the presence of various different alkaloids. Compounding this concern is the lack

of adequate analytical techniques and the variability in product content and control. Quality control does not seem to exist widely. The dangers of even low doses are exacerbated by the fact that most supplements are multi-ingredient. In total, all of this evidence does not provide me with the confidence to endorse any level as safe.

Next, since I am unable to define a safe level, it is difficult to determine a margin of safety. But food additives use a 100-to-1 margin; nutrients might go as low as 4-to-1. Therefore, a margin of safety in the range of 10-to-1 I don't think would be unreasonable.

I am unable to identify a condition of use for ephedrine alkaloids that are sold as dietary supplements. Under these conditions of sale and availability, I cannot find a use or condition or level without a risk of significant harm.

I'd like to make a general comment, if I might. I find it unfortunate that DSHEA exists. Its existence, I believe--it seems to me that it's responsible for the problems we faced yesterday and today and the lack of scientific data. It's difficult, if not impossible, to evaluate a compound scientifically which at times is a food and at other times it's a drug. I believe that if this were considered under the existing food law or the existing drug

law, we would now have adequate information to make a more reasoned scientific decision.

DR. ASKEW: Thank you for those comments, Dr. Clydesdale. It's getting close to noon. I think what we'll do is we have three people--Dr. Katz, Dr. Jasinski and Dr. Hui--who indicated that they wanted to speak. If you would like--we have a few minutes. If either of you three would like to bring your comment because it relates to something that was just recently discussed now, you can or you can wait until after the break.

Dr. Jasinski?

DR. JASINSKI: Talking about personal adverse experiences, I had an employee who worked for me who was a very loyal employee. However, she had an inherent distrust of doctors for herself. So she was 50-ish, going on, wanting to lose weight, and so she believed in herbal medicine and alternate medicine. The reason I say this is that she went out to a health food store or a herbal practitioner who told her she was going to get this magic herb to make her lose weight and sent her home with a bag of herbs--we subsequently found out about this big--and told her that she should make a tea out of this and drink it.

So she went home and came to work, and she sat at a desk all day with a very high-pressure sort of thing on

the phone and made a thermos of this and started drinking it. About noon, I get a call; Betty is having a stroke. And basically she was very fortunate because I happened to see enough people with cocaine intoxication, amphetamine intoxication, to look at this, looking at the blood pressure and doing this, and also being sensitized. For me, anything which is an abnormal change in anybody is use of a drug or drug-related until proven otherwise, just from the population I see.

So I went through the history and I said, what have you been doing. So she points out this bag of herbs and the tea, which obviously was ephedrine. So she had typical amphetamine toxicity, and basically I just sat her down and waited for it to go away. But, you know, it illustrates two problems, is that she inherently believed that going and taking this was safer than going to a doctor to get treated. So she believed this was safer. I think that's one of the inherent problems that disturbs people about this; secondly, the fact that these do have pharmacological actions, that there is no control on dose, that people can experience adverse reactions and that they're not going to be recognized when they come in because people generally don't recognize this and would have attributed this to something else.

DR. ASKEW: Thank you, Dr. Jasinski. Dr. Hui, did you want to comment at this point?

DR. HUI: Well, with respect to the use of ephedrine, my experience has been to use it in patients with postoral hypertension. They have an enervation hypersensitivity. Obviously, they came to me on these medications and the doses are usually 25 to 50 milligrams 3 times a day, but because of tachyphylaxis, you're not going to see a whole lot of effects. In terms of dramatic, exotic effects as reported, I have never, you know, seen it.

But to counter Dr. Jasinski's point, I have used herbs for than 40, you know, years. I have studied herbs, the use of herbs in pharmacology and medicine for 21 years, and I have used herbs to save a lot of people's lives when conventional medicine has not worked. And whenever you use something that's useful, there is a potential risk, and I would not use one or two cases to make, you know, a drastic statement about whether one, you know, can have, you know, herbs be available.

But I have a lot of concern about the classification of some herbs which have been used as medicinal compounds to be classified as dietary supplements. About two-and-a-half years ago at one of the FDA-Office of Internal Medicine meetings, discussing about the role of

botanicals in American health care, I'm very concerned about poorly supervised use of herbal products. With the passage of this law that allowed to be sold as dietary supplements, I know there's going to be some, you know, problems that would pop up, and we will see more of it and I just would like, you know, society to come up with a comprehensive strategy to deal with the role of botanicals in American health care and this is a good meeting to get this into focus.

DR. ASKEW: Thank you for those comments, Dr. Hui. Dr. Katz has indicated he will wait until later. Dr. Marangell, do you have a point you would like to make now?

DR. MARANGELL: Actually, a follow-up question. Are there a group of practitioners that are familiar enough with herbal medicine that could supervise the use of herbs without having to go through the drug regulatory process, but also not have them available to the whole community?

DR. HUI: Well, there are licensed practitioners, but also unlicensed practitioners in America that are using herbs. They are really poorly regulated, but at least in California licensed acupuncturists have to pass an exam that includes examination on the use of herbs and they have to study many hours. But I would say that even this group of practitioners may not be as adequately educated, and in, you

know, the situation where patients may be on other medications, I really worry about the adequacy of these practitioners' training in medicine and pharmacology and the potential for adverse drug interactions.

DR. ASKEW: We're now at 12:00 time. Dr. Weintraub indicates he has a comment he'd like to make and then we're going to break for lunch.

DR. WEINTRAUB: Yes. In terms of the point raised by Dr. Ricaurte, there was a November 1994 hearing on, in general, bronchodilating drugs and there was a lot of attention paid to ephedrine at that time. But the thrust of the meeting was on all bronchodilating drugs and we have published a preliminary rule in the Federal Register, Volume 60, Number 144, page 38,644.

DR. ASKEW: Thank you for that information. We will break now for lunch. We'll take a 60-minute break. We'll resume at 1:00. We'll resume our discussion. We'll have some more discussion and then we'll get into our summary statements. Everyone will get a chance to make their summary statement.

Thank you.

[Whereupon, at 12:00 p.m., a luncheon recess was taken.]

AFTERNOON SESSION

[1:04 p.m.]

DR. ASKEW: Okay, ladies and gentlemen, it's now 1:00 and it's time to resume our deliberations. We're drawing to a close on our two-day session concerning the safety effects of ephedrine alkaloids and nutritional supplements and food-related compounds. We had a good deal of discussion this morning, and we have a few announcements and then a clarification and then we're going to give you the opportunity for some more discussion, and then about 2:00 I hope we get down to going around the table and getting the specific response to the FDA questions. We'll do that first and then we'll go around to get everybody's individual summary statements, and also some indication of whether or not you wish to adopt the subcommittee report.

So I'm going to turn the microphone over to Dr. Larsen.

DR. LARSEN: I have a note up here and I'm not sure if I made errors in identifying people earlier by face and name connections. I have a note for Tony Young, if he's in the audience, or if anyone who knows him and sees him come in, let him know, please, that I do have this note for him.

This morning, some time during the morning during the open public hearing part, Mr. Petersen referred to a bunch of levels, LD-50s and other levels, and I did request if he would get copies to that and some time during the morning that was distributed to the committee. There's a one-page sheet that has a bunch of levels. It's entitled "Ephedrine Safety Baseline," by Gordon Petersen, or Petersen. Norwegian would be Petersen, yes, so at any rate I can say that because I'm Norwegian. And it lists four levels from the Merck manual--or four sources from the Merck manual, from Goodman and Gillman, from the American Hospital Association Hospital Formulary, and the Fundamental Applied Toxicology volume. Somewhere in all the materials, you should have that.

The other, I guess, is just an aside from what I just said. I saw folks raise their eyebrows yesterday when the lady from Delaware read the name of the inmate, and there is no conflict of interest, I assure you. I have no idea--

DR. JASINSKI: John Larson?

DR. LARSEN: John Larson, as far as I know, is no relative of mine.

With that, Dr. Love wants to make a clarification regarding the one medical record that was discussed this

morning and then I'll turn the microphone back to the Chair.

DR. LOVE: I, in fact, found out that the copy submitted to the docket didn't have all the information and I have it in front of me and would like to read what was actually analyzed by the medical examiner and found to be negative on the Florida case.

Besides the ephedrine alkaloids which you know were positive, and alcohol which was negative and caffeine which was positive, they did a number of other drug screens which included all amphetamines, barbiturates, benzodiazapines, cocaine, cann---I can't even pronounce it--marijuana, methadone, methylsqualine, opiates, phencyclidine and prophoxyphine, and then they went on in alloys for belladonna, chinchona, aragut, methylxanthine, strychnine alkaloids, amphetamine and amphetamine-like sympathomimetics, anti-antileptics, antihistamines, antipsychotics, barbiturates and non-barbiturate hyposedatives, local anesthetics, non-digitalis cardioregulatory drugs, non-LSD hallucinogens, oral hypoglycemics, synthetic anticolonergics and synthetic morphine substitute, narcotic analgesics, in addition to all salicylates--all negative. Thank you. We will put that in the docket.

DR. ASKEW: It would be hard to get a member of

our population at random and come up with that long list of names.

DR. LOVE: I would point out that these are typical screens done by almost all MEs routinely.

DR. ASKEW: Dr. Dentali?

DR. DENTALI: Yes. I have a comment on that. It would occur to me that the sympathomimetic amines should have been positive because ephedrine is certainly a--

DR. LOVE: I said except as reported as positive for ephedrine alkaloids, caffeine.

DR. DENTALI: Thank you.

DR. ASKEW: Dr. Love, as long as we're with you here, one clarification, something that arose out of the public hearing this morning. Could you comment on how some of the adverse incident reports found their way into this packet that really weren't related to ephedra?

DR. LOVE: Again, any report that has come to us we have entered into our system of dietary supplements, and it depends upon the information that has been submitted to us at the time of the report. If you look at those specific reports, some of them are on health care departments, public health departments reporting adverse events on a product where we may not have label and labeling information or there was not complete information even on the consumer

being injured.

We include any report in our signaling system. We attempt to get follow-up where appropriate. All of those reports were 1993 and prior to 1993. On the one where we knew more specific information about the consumer, we knew what she had been using prior to her adverse event, but if you look at the specific report she was at a distributor's convention when she freely sampled all the products that were available which we do not know the names of.

So we cannot verify in many cases what a consumer used. These are passive surveillance systems. We take the data as a signaling that we need to do it. When we have specific information that accompanies the report that allows us to reclassify particular products or drugs or non-ephedrine related, we, of course, do.

DR. ASKEW: Thank you. Yes, Mr. Guzewich?

MR. GUZEWICH: This is a follow-up on that, Dr. Love. Yesterday, Dr. Davidson from the Chicago Center for Clinical Research reported on his review of a number of those reports and he categorized them in a variety of ways, and I was hoping in your presentation yesterday that you might have responded to that or reacted to that in some way. In general, did you agree with his categorizations or his groupings and analysis or not, or can you comment on that?

DR. LOVE: I will just comment from the perspective of when you run a clinical trial and evaluate adverse events in clinical trial and have specific criteria for entry of subjects into a clinical trial, how you evaluate potential adverse effects is very different and there are very strict criteria to apply in these type of trials.

I do not believe that these kinds of criteria can be generally applied to adverse events that occur in a general population with random use of products that are not defined. I think that when you consider things as a risk-to-benefit ratio, of course, you always consider that in a clinical trial and you're considering the risks to the person. You have defined criteria. We don't have these type of criteria specifically in passive surveillance. They're applied a little bit more in the drug world where you have very defined products, but it's a very difficult question to grapple with when you're talking about a general consumer population.

What is significant as an adverse event occurring with a food, I think, people here may feel differently about than when you're considering it as a drug for a known indication, and that's something that all of us as physicians and scientists are trying to grapple with.

DR. ASKEW: Yes, Mr. Ford?

MR. FORD: Just briefly because as I said earlier, this whole business started--our dialogue started with the FDA a couple of years ago on these adverse reports, adverse reactions reports, and on the one hand I am pleased because--and I think the industry is pleased that the FDA did a much better job. I mean, the reports are much--we have much more information than we did two years ago on these events.

Nevertheless, it is our position that the statistics can be made to show perhaps a variety of things, and Dr. Love, of course, is part of the staff to this group and of the FDA and she has had quite a bit of time to talk about her interpretation of the reports and Dr. Davidson had five minutes. And I think if he had had an adequate amount of time--I am not a cardiologist and I don't review these reports like he does for a living and I can't really represent all of his thoughts.

I know that in our mind he raised a lot of questions, in that can all of these injuries and all of these deaths be traced to ephedrine, and our interpretation of what he told us over the course of three or four hours was, no, that there are some significant questions. And I suppose it's a mild protest more than anything else. I wish that we had had some adequate time to review the material,

but also to have Dr. Davidson present on it.

DR. ASKEW: Dr. Love, would you like to respond to that?

DR. LOVE: Just to respond to that, FDA has not made specific attribution in most of the cases and has looked at the data in its full context, considering it altogether. Very clearly, attribution on individual cases is very difficult and there are many compounders in many of the cases, but clearly there are cases that are very clear-cut--temporal relationships, dechallenge and rechallenge--

MR. FORD: Yes, there are.

DR. LOVE: -- with specific products where we have now analysis, and it's taking the data in its fullest context which we have tried to do and which we are asking you to do.

MR. FORD: Yes, and I am not--really, my compliment or maybe my gratitude is sincere. We really have been after FDA to give us more information and they have and I'm pleased with it. I would just like to have an opportunity to have an informed debate about the interpretation to get it on to the record.

And let me just add to that. The organization that I represent and the part of the industry that I represent is not here to say that these products that you're

looking into should be equated with mother's milk; very far from it. We are not here to say that every product, because it's natural or whatever, is safe in every case. We do think we have some evidence of safety. We do think we have some evidence of efficacy, but efficacy is not the issue here and we well understand that.

But I want you to know that the industry is trying to--the responsible part of this industry wants a solution to the problem and we don't think that an outright ban on a product based on the information that we're supposed to process here over two days would be the right way to go. I'd like to see the industry have an opportunity, perhaps a window of some kind to see where an appropriate solution lies that would satisfy most parties.

DR. ASKEW: Thank you for those comments and, of course, this committee is not considering the specific question of an outright ban of this product. I hope everybody here realizes that. Based upon the questions that we have been asked to consider, we're giving our opinion on some safety aspects.

I know there are other people that want to continue the discussion and we will, but Dr. Croom has something he would like to bring before the group. Dr. Croom is a professor of pharmacognosy and he has some

statements, and he was also a member of the original working group and he has some information that he thinks may help us a little bit in our deliberations.

Dr. Croom, and then we'll go to the rest--we'll throw it open for open discussion.

DR. CROOM: Thank you very much. I want to go ahead and share with you a perspective. I've tried to look at this from a safety point of view and just as if I was teaching, as I've mentioned, and writing a monograph that takes a holistic approach, not just one thing.

I say that--I'll preface it with saying that I'm convinced there's enough data to say that there are some people receiving utility from these products, and therefore it's worth looking at what are safe levels. Now, let me say from things I've seen the last year, even since our committee, when we talk about dosage at this point, let me say I would go lower and that I would recommend, if I was doing the recommending, for total ephedrine alkaloids 10 milligrams per dose, which is at the low end of even combinations, 40 daily, and for ephedrine 8 milligrams a dose, 32 daily.

Some of that is hearing the Canadian experience and some of that is going with when I'm looking more and more at safety here, the pediatric dose for ephedrine is

6.25 to 12.5. So I'm taking some of those things into consideration and for--some of the efficacy of products I know, not just for weight loss but for asthma, are around 10 to 12 milligrams.

Now, what is the rest of the mix? GMPs, rigorous GMPs, have to be in place for this work, and I consider that meaning from the absolute identity of the plant species to the quantitative analysis of the final product. There's a second bullet under GMPs I want to highlight, and that is it has to be certifiable. My point is if product variation is occurring from other places, the marketer-manufacturer better have an independent, certifiable program to tell me that that quality of that extract is not just what we normally do by GMPs. I'm not going to recommend any more details, but to say there has to be a certification program for this to be worth the paper it's written on.

I truly am putting the criteria--I have a 17-year-old son who likes to lift weights. I have a 9-year-old daughter. I'm trying to come to the criteria that I would think that if they ever came across this product, what would help protect them now or in the future.

The next thing I would say is formulation. To enhance safety, I think from the data to date I would say no xanthine alkaloids in any form, no stimulant laxatives, and

no ingredients, of course, that are MAO inhibitors. In the final product form, what am I looking to enhance safety there? I don't want anything that could be easily misused or overdosed by the patient.

So, again, I'll reiterate what I wrote the committee last year. No beverage form or drink, including powders, to make a beverage, nothing that can be confused, like I'm drinking this as a beverage; no form that resembles a food, snack, gum or candy; no chocolate bars, no energy bars. That's the kind of concrete things I want to see done. Label warnings--all OTC warnings for health conditions and drug interactions and populations at risk.

I'm sorry. The data to me says use less than seven days, period. If you go beyond seven days, we do not know the effect of these compounds on decreasing your heart capacity over time. I do not think that data is there. The other thing, because they're sold as dietary supplements, let me say, is I want to avoid anything that would give a claim, but I think we should state what is the physiological activity of this. It stimulates your heart, the central nervous system, and raises your blood pressure.

In other words, you should know if you take this, here are the physiological consequences of what you're going to do to your body. And I'll tell you, if you like to play

tennis or lift weights--tennis is more what I like--you know that your heart rate is going up and you should warn with accurate information what's going to happen.

The last thing I want to say is labeling and promotion. When I review the adverse events, it is not products for asthma, colds, not only those given by Chinese practitioners. There are others on the market, so I say no product names, labeling, or promotion for euphoria, energy, stimulant, weight loss, ergogenic bodybuilding, or enhanced performance should be part of any promotion or labeling, including your name. In other words, you take it back to where anyone who's using this in the time before we had all these adverse events and we see can this level of responsible use of ma huang--when you take traditional uses, when we take the medical uses of these compounds, can we handle that with this high quality for dietary supplements?

This is when I say it has to be an overall effect because if you're going to promote--and I walk in a store and see a ripped guy's muscle, a beautiful woman, all of these things coming in to say "take ma huang," no. I think this is very, very risky behavior.

DR. ASKEW: Thank you, Dr. Croom. Now, we're going to open it up for general discussion. Anyone can comment that wants. Dr. Jasinski and then Dr. Applebaum.

DR. JASINSKI: Yes. Coming back to Dr. Love, and I don't doubt Dr. Love, but, you know, the critical question has been the relationships of these deaths and your data and the particular interpretation versus the interpretations we've heard, and there has been a conflict. And since we're supposed to be here as scientific consultants in viewing this and we have a scientific philosophy and culture, one of the questions I would ask, if it has been done--if not, I suggest you do it--have you taken your data--I mean, in science we collect data, we analyze it and we make conclusions, and the essence of the scientific culture is we have peer review.

Now, we've heard you present the raw data and we've heard you present. My question is have you prepared a report on your data, how you collected it, how you interpreted it and what conclusions you've made, and have you submitted this to internal review within the agency or outside the agency? And, similarly, have you taken the report from this ad hoc committee and submitted it to a peer review?

I mean, to me, that is very sort of critical because I'm in the position of trying to make a peer review judgment and I'm not sure, you know, of the data and the process in it. That's what I feel uncomfortable about.

DR. LOVE: We, of course, intend to do that, but we were analyzing this data even over the weekend to supply the information to you at this committee meeting here.

DR. ASKEW: Dr. Applebaum and then Dr. Blackburn.

DR. APPLEBAUM: Thank you. I just need a little bit of clarification here. I appreciate very much Dr. Croom's comments because they help clarify the situation. However, Dr. Kessler earlier today prior to our lunch break said the committee is to consider the safe level in the context of the diet, and when I hear the term "diet"--and I want to make sure I'm not incorrect--I usually tend to use the adjective "daily" in front of the term "diet" because the diet is taken on a daily basis and you're recommending that in terms of the guidelines, or at least the labeling, to take this dietary supplement no more than--no longer than seven days.

DR. CROOM: No more than seven days, and certainly no more than four times a day as any daily serving, of course, was our question as a dietary supplement. This is not a diet. This is a dietary supplement. My understanding is botanicals are dietary supplements. This is a botanical. We're not talking about foods, we're not talking about drugs. We're talking about dietary supplements, botanicals.

DR. APPLEBAUM: So then in the context--I need

clarification, then, in the context of the diet.

DR. ASKEW: How many times a year would you supplement for seven days with this, Dr. Croom?

DR. CROOM: I don't know how many times you get a cold or asthma, or whatever. I mean, I'm going by the guidelines that, to me, again we see for whether it's the traditional uses, the Canadian experiences, our experience with these. They're always short-term, they're always less than seven days. That's the standard guidance. That's the basis for that.

DR. ASKEW: Dr. Blackburn?

DR. BLACKBURN: I liked Dr. Croom's suggestion, too. It tends to bring us toward a center and it tends to elevate the quality control and production and advertising and promotion of these products, and it tends to bring Eastern and Western medicine a little close together. But I think before we accept the valid use of these in any traditional sense at all, we need to be guaranteed the quality control and we need to see evidence that evaluation of these products is made by systematic observation and experiment.

At the other end of the spectrum, the issue of euphorics, the Commissioner has very effectively, I think, used the weight of his office in the FDA in a very

legitimate way and gone to the public in today's paper in labeling the use and the promotion of Herbal Ecstacy as irresponsible. I think that's a very appropriate use of FDA authority.

I think it remains for us to touch on the issue of whether its use, as Dr. Croom suggested, for performance and for weight loss is also irresponsible and whether we would advise in the warnings that it's undesirable, at least, to accept under medical supervision. And, finally, as a general comment I think all of these issues raise the issue of whether FDA should consider how better to regulate these products and their promotion of any highly pharmacoactive substance as a food supplement or additive.

DR. ASKEW: I would like Dr. Bruner to perhaps think about addressing the responsible use of these products with regard to a weight loss program and offer some comments, but I think Dr. Kessler may have had a comment he wanted to make before that.

DR. KESSLER: It was just a very minor point, Dr. Applebaum's point. I think I said in the context to supplement the diet. As opposed to in the context of a diet, it's in a context to supplement the diet. Maybe we're saying the exact same thing, perhaps, because if you're going to supplement the diet, then you're in the context of

the diet, but it is not in the context of colds, asthma, therapeutic indications.

DR. ASKEW: Dr. Bruner specializes in bariatric medicine and family practice and has had a good deal of experience with counseling people with regard to weight loss and perhaps she'd like to share some of her experiences with us.

DR. BRUNER: Well, thank you very much, Dr. Askew. First, I'd like to say that in working with obesity and obese patients, I think the use of ephedrine saying it's a dietary supplement is almost an oxymoron. So in any event, I'd like to share with you what I do just very briefly in four case reports that I have.

In screening patients initially when they come in, they get comprehensive history, physical, laboratory examination, and that's basically before the onset of any kind of intervention. And I do have four current patients I'll share with you just briefly who are currently taking ephedrine. Now, in my practice I use, certainly, other agents, but these particular ones are on ephedrine.

I had a 16-year-old young lady who came in in the first part of April. Her BMI was 40. She was five foot, four, and 230 pounds, with a strong family history on both sides of obesity. Now, in this particular patient--and

before we start therapy, we do have informed consent and that's part of what we do, is explaining risk of side effects and effective usage, and certainly in a medical practice one can do that because you are screening people.

And we started her off with a 12.5-milligram dose of--it's an ephedrine hydrochloride; started it out on a BID dosage and a 1,400-calorie diet along with exercise recommendations and water. And actually she weighed in last week at 198 pounds and really has suffered no ill side effects, no significant side effects, complained of no CNS effects.

I have a 54-year-old woman who's 5'2". Her BMI is 31. She tried a number of other weight loss programs and also had used amphetamines back in college days, was not interested in any kind of controlled substance, and we started her off on ephedrine 25 milligrams TID. Now, she did complain of some insomnia initially and we just had her adjust her dose to a little earlier in the day and she's currently weighing 140 pounds.

Another case of a 39-year-old with a BMI of 37 who had an inability to lose weight, had followed other programs, actually has a Ph.D. in nutrition, is an RN also, and certainly is well educated in terms of behavior modification. I suggested that we try a thermogenic agent

as ephedrine, and even though she has only lost about 10 pounds, this is 100 percent better than she has done in the last 5 years. She did have some acne of rosatia which has been a little bit exacerbated, but she is tolerating that effect.

And also a 37-year-old woman who's 5'6", a BMI of 35. She was on the phen-phen protocol, phenfloramine, phentromine, by a private physician, but with no counseling; was not interested in trying any other agent. And we put her on ephedrine and she has done quite nicely. This was in the first part of May. She's down to 185 pounds.

So I think what we're seeing in the treatment of weight loss is certainly an armamentarium that we have, and frequently with the regulatory boards in terms of state boards of medicine they wanted to regulate and legislate our practices and our ability to prescribe medications without getting the facts. And I think we've had a lot of information that has been disseminated to us here. If we review the literature in terms of weight reduction, looking at caffeine, ephedrine, and aspirin combination that has been highly publicized by Dr. Astrup and some others in England, Dr.--I'm forgetting his name--Homer--we're seeing some studies. Granted, they are some short-term studies with few patients, but if we look categorically at them,

they're losing weight.

We are not reporting, per se, the incidence of side effects exactly. They do, in general, note that--Dr. Astrup published in 1990 in Current Research Therapeutics that actually 10 milligrams of a TID dose of ephedrine was successful in weight loss, and so we're seeing certainly that there is some efficacy. And I think what I'm saying, we shouldn't throw the baby out with the bath water. If there are certain mechanisms to regulate and to assure the quality of the content of these agents which we don't have in place now and which I'd like to ask the FDA--do they have mechanisms by which, if we had recommendations in terms of manufacturing, that could be in place, because I think that's critical to what happens, and as Dr. Croom had suggested, not adding certain items because we know, for example, alpha 2 agonists like chlonodine, if given with ephedra, had potentiate hypertension, as can yohimbe. So if we can assure unadulterated products, I think we can make a better case for their usage.

DR. ASKEW: Thank you, Dr. Bruner. Dr. Ziment?

DR. ZIMENT: I liked very much what Dr. Croom said and I think what Dr. Bruner also said has merit. However, two things that Dr. Croom said that I don't quite understand. One, he said the dosage should be limited to

seven days in these regulations, and I don't see why and I certainly don't quite understand what he meant about the effect on cardiac capacity. I think that was the term he used. I don't think that that's necessary exactly what you meant. It still leaves me with concern that this implication that more than seven days could be hazardous, as opposed to less than seven days in some sort of long-term fashion. I just don't see the evidence for that. That's number one.

And number two, very briefly, I think you implied that this recommendation would encourage, perhaps, the regarding of ephedrine as a drug for asthma and for the treatment of colds rather than for other uses. And I just would point out that the NIH in its guidelines which it has worked so hard to promulgate for physicians across the country does not recommend the use of ephedrine for asthma. Moreover, there are far better remedies for the treatment of upper respiratory infections or colds than ephedrine.

DR. CROOM: I'll let some other specialists--but let me address a little bit of that. What I'm trying to look at is we have a lot of long-term use under those conditions which were seven days or less, because my feeling that I'm looking at is the safety and that's the major thing there.

The cardiac I'll let our cardiologists speak more to, but let me say that even though in the weight loss regimens--I think for self-treatment with a dietary supplement, to have an open-ended use policy for something this potent is just not wise. It's just not wise, and when you are stimulating the heart we've heard the case, I thought, given of wasn't this contributing to the death, possibly, of this person. Is this not right, Dr. Love, that as far as--the cardiac necrosis, I thought, was the term used in this death of this tough student. Is that not right? And because amphetamines can do that, it's not clear to me what chronic, long-term use of ephedrine--

DR. LOVE: Ephedrine is also recognized.

DR. CROOM: Exactly, in this case for your capacity over time, if that's a wise practice. So that's why I'm asking for a limit on any time frame. I know you know the--both of you all were going to speak.

DR. ASKEW: Yes. Donna Richardson wants to comment and then we'll go to Dr. Inchiosa.

MS. RICHARDSON: I'd like to say that I like a lot of what Dr. Croom says. I think certainly if you're talking about a seven-day limit, then the packaging has to accommodate that seven-day limit, that that's all will be in that packaging is seven days.

I guess what I have picked over the last couple of days--and I was on the working group--is that we have what are called supplements to the diet and they contain this entity that has also been called a drug over and over over the last two days. And then we are blaming the consumer because they're misusing this diet supplement. They misuse it, they abuse it, they overdose on it at the same time that it's being marketed as a health food. It's something natural and they're going to have a perfect body. Either they will become slim or they will become Adonis. But the labels are obscure and they're not direct.

You know, I liked what Dr. Jones said about using this may cause impotency, but I think it should also say more than don't use this if you have heart disease or thyroid disease because what does that mean? I think it has to be explicit that people are going to have seizures; they can suffer a stroke or a heart attack.

I've heard the side effects called "expected" and someone even called them minor because there are no lasting effects. Well, there are some lasting effects. Any application you fill out for health, life or disability insurance and for a job says, have you ever had a seizure, have you ever been told that you had a stroke, have you ever been told that you had a heart attack, have you ever had

hypertension. Try and get life insurance or disability insurance after you have answered yes to those, and especially if you suffered those when you were young. I think the labeling is not enough unless it is just as prominent as the claims.

The other concern that I have is that we talked a lot during the working group about education, and I think it's education of more than just the consumer. I heard I think it was Dr. Ziment say that all of the physicians know about ma huang, they know about ephedrine. But what we talked about during the working group is that they don't necessarily know about diet supplements, so that when a patient is in and they're asked what medicines they're on, they're not asked, are you taking any diet supplements, are you taking any health foods.

And so often the physician, nurse midwife, nurse practitioner or the nurse taking that history may not ask that question. So we've got to educate physicians and other health care professionals. That includes the psychiatrists and the counselors because of the psychiatric implications of these diet supplements. And I think we also then have to look at educating the educators, since we are talking about a young population that has a tendency to misuse these entities. And the other group is coaches. If indeed it's

being promoted as a body enhancer, then the coaches also have to be educated about this drug, and that's what I'm calling it, is a drug.

DR. ASKEW: Thank you. Ms. Richardson is our consumer representative and her views are particularly valued with regard to the consumer and how the consumer might react to these products.

I'd like to go now to Dr. Inchiosa, then Dr. Ricaurte; Dr. Benedict, who also would like to comment; Dr. Marangell; Dr. Hui. We'll go to Dr. Inchiosa.

DR. INCHIOSA: I wanted to talk about briefly your recommendation or suggestion of 10 milligrams per dose. Also, it seemed rather a cumbersome procedure that would be required for guaranteeing the safety and the quality of these products, but also then you begin to mention all the things one could not claim and so therefore you're not claiming any therapeutic benefit, no weight loss. So it ends up really being just a dietary supplement of rather not well-defined value or indication, or value, let's say, because at the end of the all the exclusions I wasn't sure really how this would be advertised. So, that's one aspect.

But regarding the 10-milligram dose, 10 milligrams of ephedrine is a significant amount of ephedrine. It's rather interesting. Since we're talking about science, you

can only really see the cardiovascular effects, the true potential of those 10 milligrams in a hypotensive individual. And it turns out that ephedrine is the mainstay, the most popular drug used by anesthesiologists to support blood pressure induced by inhalation anesthetics, by regional blockade of the sympathetic nervous system.

Under those circumstances where you have vasal dilatation and a decrease in cardiac output, ephedrine is the most popular drug selected by anesthesiologists. Under those situations, 10 milligrams of ephedrine administered intravenously produces a very dramatic increase in blood pressure and return. So it increases cardiac output, increases venous return, and so you get a dramatic pharmacological effect. The fact that you don't see that effect in a normal tensive individual is because of reflex autonomic influences. So you get a reflex bradycardia, but you still have vasal constriction.

And so therefore you're talking about a situation where you have--normal tension may remain, but you have constricted the mesenteric beds. But one should not be fooled by the fact that there are only modest changes in blood pressure in a normal tensive individual. In a hypotensive individual, this is a therapeutic dose being used now in the operating rooms on thousands of patients as

we sit here talking that are supporting blood pressure. So it's a very important drug and its true effects can be seen there.

Regarding that other statement you made about the seven days, I think that the seven days is fine when you're talking about it in a therapeutic context. If you were to say that you were going to try a short therapy, self-administration by a person to try a medication for their asthma, seven days is good limitation because then they should seek medical advice if they don't get the desired therapeutic result.

But if this is now then truly a dietary supplement, saying seven days seems to be a contradiction if you're looking at something which is a tonic, something which someone is taking for a tonic reason. And there the chronic beta 1 stimulation is, in fact, going to cause beta receptor down regulation, and your comment about a decrease in contractility would, in fact, be expected because of beta 1 receptor down regulation on chronic use.

Also, in that dosage range, and especially--it's interesting, and one of the most dramatic things that struck me when I read the reports and the advertisement is that this drug is suggested as being used in conjunction with training, physical training. It is the worst drug to use in

conjunction with physical effort because it increases release of catecholamines. Exercise is going to increase sympathetic discharge, so you're going to have a synergism of the body increasing sympathetic drive, increased release by ephedrine.

It prevents the reuptake, which is the major mechanism for clearing norepinephrine and epinephrine from the bloodstream, and it also interferes with the--it inhibits the metabolism by monamine oxidase. So one has a very unsafe combination of effects and therefore one would expect under these circumstances myocardial necrosis with prolonged even low-dose use because of that chronic concentrating effect.

MR. CROOM: So would you change the number of days or would you leave it--

DR. INCHIOSA: No. I think the number of days is good, but I think it has to be done, which I've mentioned before--I think this drug should be used in a therapeutic setting with an indication, a clinical indication for its use. I think that's the only safe and appropriate use of the drug.

DR. CROOM: And the other thing, again, I want to point out on the dosage recommending--I'm going by where do we have the longest safety data. The Chinese herb itself

has between generally 1 and 2 percent. An average dose of the herb is 6 grams. That means you have between 6 and 12 milligrams of alkaloids there. So I'm taking traditional long-term use, what do we know from others, not to justify the use, but to say for safety where are the numbers, and yet not get to the point to where if people are taking it for some utility, no matter what, that we're balancing about--that we're, to me, saying as even a naive user, how can I try to set a safe level, but give some utility.

DR. INCHIOSA: I agree a hundred percent with you. I think that your dose in that range, somewhere under 10 milligrams per dose, would be an appropriate therapeutic dose, with supervision. I agree completely. It's a good dose.

DR. ASKEW: Dr. Kessler has a comment and then we have some other comments.

DR. KESSLER: Just a question on this point for those who are experts in how dietary supplements are used. Not on the medicinal side but as a supplement to the diet, is it common to think about a supplement to the diet being used for a limited period of time to just 14 days?

DR. DENTALI: Yes.

DR. KESSLER: Are there other examples where you use a supplement for a limited period of time?

DR. DENTALI: Most tonics, a seasonally limited time. Akinesia is a classic one. Most every herb I use, I don't take herbs on a daily basis. I almost only use them for limited periods of time. There are many others that would be used for longer periods of time. I don't personally happen to be doing that presently.

DR. KESSLER: And the other one is a very simple question just for the record. As a supplement to the diet, what's the purpose of the ephedrine?

DR. DENTALI: For myself, I suppose--I'm a hay fever sufferer. I am impressively sensitive to grass pollen. I got desensitization shots as a youngster, left the country and stopped that, and I was pretty okay until I moved to Oregon. I suffered through one summer. The next summer I broke down and took all the available drugs I could get my hands on, and the next summer I started the program again.

One of the things that I have available to me is a one-ounce bottle of ephedra extract. It's a pure alcohol-water extract. I haven't used it in two years, but it's something I would like to be able to go, if I chose to, and take a few dropperfuls of that and see what the response is, and this is generally how I would use the drugs as well; try it, see what the response is, see how I tolerate the side

effects, see what the efficacy is. So in this case it would be promoting open air flow during times when I felt that that was necessary or desired.

Granted, I don't think that really a dietary supplement is an appropriate place for herbs or herbal extracts, but it happens to be the only regulatory place we have for it right now.

DR. KESSLER: We're seeing an increased number of products that have ephedrine-like compounds and I guess the question is why is that, why is the ephedrine there.

DR. DENTALI: I think it's quite clear that a lot of these products from the good work that Dr. Love did are in the weight loss category, and it's not just for ephedrine. It might be instructive to look at the categories that products are being made. I think I could give other examples of products being used for weight loss that are inappropriate and dangerous as well.

DR. ASKEW: We have several people waiting to speak. Dr. Ziment, I think, has something on this point. Do you?

DR. ZIMENT: Well, three minor points. One is there has been some speculation about myocardial necrosis occurring as a result of using beta 1 or beta 2 stimulators. There's a long and very detailed knowledge on this problem

and it turns out that the damage to the heart by the use of these agents is extraordinarily rare, very rare indeed, and that there are just case reports, such as somebody using isoproterenol by metered dose inhaler and using something over 50 puffs a day, which is well beyond the recommended dose, leading to myocardial contraction bands and myocardial infarction. Even arrhythmias are rather rare when using beta agonists, unless a person is also hypoxic or hypokalemic. So I'm not really worried about ephedrine causing long-term cardiomyopathy or short-term myocardial necrosis if used within reasonable, appropriate dosages.

Secondly, I'm concerned about even the suggestion that an asthmatic should self-medicate themselves with an ephedra product for seven days with mild asthma. That is not mild asthma. Mild asthma responds to one dose or two doses. If a patient needs it for seven days, they need to be seen by an experienced practitioner, usually a physician, who will then introduce appropriate medicine which may be anti-inflammatory and not just beta agonist.

And alongside this I also worry about utilization in the treatment of colds and allergy for a week because a cold, again, probably needs less treatment, unless it's sinusitis and has complications, whereas allergy is likely to go on for much longer than a week and people will tend to

have to treat themselves maybe for a month. So, again, the seven-day figure is one that sounds good. God created the world in seven days, or he rested on the seventh day, and I guess that's where the inspiration for seven days came from, but there's no other pharmacologic reason that I know of.

DR. ASKEW: Thank you, Dr. Ziment. Dr. Kessler, did you want to respond?

DR. KESSLER: Just to emphasize and to agree with that point. The Food and Drug Administration--we agree wholeheartedly; ephedrine is not the standard of care for the treatment of asthma. There are effective medicines over the last several years in the treatment of allergic rhinitis. Also, we've seen dramatic increases in how to treat those conditions. The Food and Drug Administration does not believe that these medicines are appropriate, certainly not the standard of care in those diseases.

DR. ASKEW: Okay, folks, it's getting close to 2:00. At 2:00, we want to start our polling, but I've got a number of people here that have asked to speak and so I would like to give them an opportunity and to be brief. We have Dr. Ricaurte, Dr. Benedict, Marangell, Hui, Hsieh and Jasinski. Is that right? So we're going to go in that order, and make your comments brief, please, and go ahead, Dr. Ricaurte.

DR. RICAURTE: A question to two of the previous speakers. If the indication is not weight loss, it's not stimulation, it's not body-building, what is the indication? I guess I would direct that to Dr. Croom or people with the manufacturer. I want to make sure I understand Dr. Kessler's point. He says use of the product as a diet supplement. Is that specifically with relation to weight loss or not, I mean, because it may help answer the issue of how we should assess the use of these drugs?

DR. YETLEY: That's language from the definition of a dietary supplement in the law which says that one use is--its purpose is to supplement the dietary intake of a particular substance.

DR. RICAURTE: But we're not to link that with weight loss?

DR. YETLEY: The statement--I could read it for you. I think it's here. I'll see if I can find it quickly, but it's not linked to anything in the Act. It simply says that's a purpose of a dietary supplement. Now, whether or not you want to link it to one of these, I think, is another issue.

DR. ASKEW: Dr. Benedict?

DR. BENEDICT: Three very brief things. One, will we have the opportunity to make a statement, in addition to

being polled?

DR. ASKEW: Yes. At the very end, you're going to have an opportunity to make a summary statement.

DR. BENEDICT: Thank you. The second thing is I'd like to applaud Dr. Croom for giving us a point of debate that we could all discuss. And with respect to that, with respect to the seven days, did I understand Dr. Love to say that least 50 percent of the adverse reports occur at very early times, usually less than seven days?

DR. LOVE: What we see in our data is about 13 to 14 percent are in the first use or first day of use and about 35 percent, about a third, within the first week.

DR. BENEDICT: Thank you.

DR. ASKEW: Dr. Marangell?

DR. MARANGELL: Yes, a point and then a question. I'm glad that someone brought up psychiatric side effects of these medications, as well, and adverse events. We haven't discussed that very much and it doesn't often lead to death, but in terms of looking at at-risk populations I would appreciate it if people included the 1 percent of the population that has schizophrenia, which certainly can be exacerbated by these products; the 1 percent of the population which has bipolar disorder, which can be exacerbated by these products; all the additional patients

that have panic disorder and generalized anxiety disorder. And at a minimum, I'd like to see the labeling reflect the potential risk to those individuals.

I have a question. When we're trying to set what is the safe level, and whether it be 10 milligrams or 5 milligrams or 20 milligrams, I am caught because we're extrapolating from the pharmaceutical. And I've heard the discussion, and please correct me if I'm wrong, I don't understand how you can do that with these products.

DR. CROOM: I have to qualify that.

DR. MARANGELL: With the variations in the assays and Dr. Love's presentation on even within the same product there's a tremendous changeover time--

DR. CROOM: I gave you the standard range of 1 to 2 percent in the herb, not the drug. That gives you a dose between a standard use that has been used by thousands of people for 1,000 years.

DR. MARANGELL: Well, but--

DR. CROOM: No. It gives you a dose range of 6 to 12 milligrams on a standard dose, even taking in all the variations we're talking about.

DR. MARANGELL: Okay, but you're also extrapolating from--

DR. CROOM: It's only herb.

DR. MARANGELL: --the pediatric dosages of ephedrine.

DR. CROOM: No, no. This is from the plant ephedra. That dose I'm giving you is on the herb itself.

DR. MARANGELL: The herb itself as it has been used was under the supervision of practitioners as a medicinal--

DR. CROOM: Not necessarily. That has been presented here. It is by practitioners. It also a patent medicine in China. It has also been on the market in this country for a number of years for self-treatment without a wise guru always directing you to its use. It's common for self-treatment also.

DR. DENTALI: I have a comment on those figures.

DR. ASKEW: Dr. Dentali wants to jump in at this point.

DR. DENTALI: Yes. Now, correct me if I'm wrong here, but we're talking about 6 grams at 1 to 2 percent. My math comes out to 60 to 120 milligrams. Please correct me if I'm wrong there. 6,000 milligrams at 1 percent; 10 percent of 6,000 is 600; 1 percent is 60. Double that is 120, so you're underreporting by a factor of 10.

DR. CROOM: By a factor of 10, that's right.

DR. ASKEW: Would you clarify that again for us,

Dr. Croom, what you just discussed about the underreporting by a factor of--for those of us that are less nimble following the calculations?

DR. CROOM: Okay, let me explain that. In the herb itself, that is correct that of the figures that Dr. Dentali just said it's 10 times the amount I did. Now, let me say, though, that I don't think you extract everything in the herb, and so you're right. I should have clarified. My figure was 10 times less to say that that's even the amount that you would be getting in the water, in the tea, instead of the herb itself. That is correct and that's the amount that would have been at the minimum ingested.

DR. MARANGELL: I still don't understand how you're going to set a commercial standard when you don't have a reliable assay that takes into account all the various alkaloids and different matrices. How is that possible? How is it that there's such variability from one product to another that you can set 10 milligrams and know that that's what it is?

DR. CROOM: Remember, part of the package that I've presented is GMPs with a certifiable, quantitative analysis of the final product form. In other words, if there's not such an analysis and it cannot be done, then you can't meet the GMP.

DR. MARANGELL: Well, that's my question. I wasn't trying to--

DR. CROOM: There's at least 5 or 10 assays besides the ones presented here, by the way, on quantitative HPTLC in capillary electrophoresis. Part of the problem you're seeing--their product variation is they're having to analyze every product under the sun, no matter what's put in it. That's an impossible quantitative method. The herculean job done by the FDA has been amazing on these analyses, and so my point is for industry to do this it's going to have to have a reproducible, quantitative, rigorous assay to answer that question.

DR. MARANGELL: I agree.

DR. ASKEW: We'll go to Dr. Hui next.

DR. HUI: Well, first of all, I think the figure that Dr. Croom put together again is for the use by the Chinese practitioners and it's a dose arrived at over centuries, but it's used usually in combination with other herbs that may counteract the side effects of ephedra, and I think I want to, you know, make that clear. And also it's used really to bench the possible physiological state of the patient at that point in time and it's used with adjustment according to the patient's response.

So it's not going to be used like over a certain

period of time on a regular basis, so I don't know what will be, you know, the right length of time. I don't think it should be used on a chronic basis. In terms of indications, this is supposed to be a dietary supplement. We accept that this does not have any value in terms of diet, but that since it's used by our citizens to improve their well-being--I suppose a lot of them take dietary supplements to improve their well-being in their perspective maybe to fight fatigue, maybe to help them, you know, decrease weight. If that's, you know, what Dr. Bruner and other researchers have found, then we will have to accept that this is what they are going to do. If we ban it, then they will go underground and so we have to come up with something that is safe.

I don't think that those that Dr. Croom suggested is safe because I really think that we have to take into account a lot of the concomitant factors that may affect the response to the amount of ephedrine that's being used because a lot of our patients, our citizens, are under a lot of stress with restructuring and downsizing. And we also have to recognize that they are also drinking a lot of caffeine and they may be taking antibolic steroids to increase, you know, their muscle mass. Again, they are exercising. That may increase their adrenergic stimulation.

So I think that the dose has to go down, you know, by a factor, and even 10 TID, assuming that the Chinese use 60 milligrams, total, so it's 20 TID--10 is half, and I have heard about a five-fold difference in terms of the variability in the clearance. I have heard about at least an arbitrary figure of 10 percent, so it would bring it down to even lower, the 10-fold decrease. So that will make it down to 2 to 4 milligrams each unit dose, and I recommend a lower dose because I think that most people, in general, would use more.

I mean, that noncompliance in this situation is to take more, not to take anything for a condition that people want to see results. You know, for pain and for results, people, in general, take more, so I would suggest that if we decide to keep, you know, the product on the market that we should try to bring it down; you know, maybe 2 milligrams, at the most, 3 times a day, and that if they are to use it, you know, on a more chronic basis and if they have any side effects, they need to consult any licensed practitioner who is knowledgeable in the use of this substance.

DR. ASKEW: I'd like to remind the committee members that you're going to have an opportunity to give--everybody is going to have an opportunity to give a recommendation with regard to the dose level when we go

around and then poll everybody. Dr. Hui has introduced the stress factor and a number of us have airplanes that we've got to catch this afternoon, so excessively long comments at this point increase our stress factor.

We have three people left to comment--four, counting Dr. Ziment. I would ask you to be extremely brief because we do need to get into some resolution for the FDA on this. Dr. Hsieh is next.

DR. HSIEH: You can regard this as a part of my later statement so that I'm not taking any extra time.

DR. ASKEW: Good.

DR. HSIEH: In light of Dr. Croom's dose and duration of dosing and Dr. Hui's modified figures, I want to share the figures that I have stuck my neck out to come up with. The bottom line is 2 milligrams per average person per day for unlimited use, and this is based on the safety assessment guidelines, the federal risk assessment guidelines approach. And in this approach, we use the uncertainty factors, as most of you are familiar with, and there were four areas, four extrapolations that the uncertainty factors are applicable.

The first extrapolation is from animal LD-50 to no observable effect level extrapolation, LD-50 to NOEL extrapolation. That's number one. Number two is

extrapolation from animal to humans, and number three is extrapolation from an average human to a sensitive human, and then number four is extrapolation from drug to food. These are the strategies that I used, and the data I used was I came to this 2 milligrams per person per day from two approaches, two scenarios.

Number one is using Dr. Petersen's LD-50 value, which is 360 milligrams per kilogram LD-50 in rats. So you extrapolate from the animal LD-50 all the way to dietary supplement for sensitive humans and you use the uncertainty factor. Usually, the uncertainty factor is a value from 10 to 10, and for conservatives purposes I used 10 on each of the extrapolations. So the total uncertainty factor becomes one-tenth to the fourth power, and if you do that, then 360 milligrams per kilogram is translated to 0.036 milligrams per kilogram per day for a sensitive human using this compound as a food supplement. And for an average person weight 60 kilograms, a 60-kilogram body weight, then the average daily dose will be 2.16 milligrams per person per day. That's my first approach.

The second approach is taking into consideration the dose of ma huang that was quoted by Dr. Croom

being 9 grams per day per person in the traditional Chinese medicinal practice. And I'm using the 2

percent ephedrine alkaloids content as given to me by Dr. Obermeyer of FDA, so the average person per-day dose is 180 milligrams, 180 milligrams per average person per day. And because in this case you only extrapolated twice from average human to sensitive human and from drug to food, so you multiply that one-tenth to the power of 2, namely 100. So you come up with 1.8 milligrams per average person per day. So from these two figures--one is 1.8, one is 2.16, so I just round it up at 2 milligrams per person per day. And this kind of elaboration is a safety evaluation, so it is for the daily intake kind of scenario.

DR. ASKEW: Thank you, Dr. Hsieh, for that detailed and well-reasoned calculation. Let me move now to Dr. Jasinski, then Dr. Wang, and then Dr. Ziment.

DR. JASINSKI: I'm going to go back to a question, many questions Dr. Kessler asked or put on the table--

DR. LARSEN: I don't understand why your microphone--but these are voice-activated microphones, so please get close.

DR. JASINSKI: --people would take this as a dietary supplement. To me, it's very clear, okay, and it's basically what I've spent my career doing is finding out why certain substances are reinforcing in psychopharmacology in certain substances or not; that is, within our society we

have certain substances which are reinforcing certain chemicals or substances. I mean, years of research--the consensus is they have certain properties. They are psychoactive in that they alter mood, feeling, thinking and perception. These contain ephedrine. They are taken to doses which are psychoactive in these dietary supplements.

In fact, if you look at the character of the psychoactivity, it produces a typical amphetamine-like profile. Now, in this, from studies which have been done, if you give drugs of abuse to, quote, "normal population," most people like the effects of amphetamine if you keep the dose low. It gives them feelings of increased energy. It raises their mood. It has some analgesic action, gets rid of aches and pains. They feel they can perform better and they last longer. You may, you know, drink a diet Coke to get a little bit of cocaine--I mean coca, caffeine, in terms of this.

And the issue is if you look at why these are popular in the stores and why there are so many preparations, it's because of what people are buying and the consumers are taking and the fact is that of all of the products that are sold there, this is the one that's going to deliver as a dietary supplement. If you take it, you are going to feel it and you're going to feel better. You're

going to feel like you're taking something that's giving you increased energy and all of the things that delivers on what it promises.

DR. ASKEW: Dr. Wang?

DR. WANG: I'll just make it short. Again, I agree with Dr. Croom. Maybe regarding combination products, since we have seen a lot of the adverse reactions, adverse events--the majority of events were due to combination products and I think that really needs to be considered, reformulate without, you know, stimulants with that, again taking into consideration the dose.

I thought since in the OTC drugs ephedrine is allowed to consume, what, 150 milligrams per day on the sustained release product, maybe a 10-fold safety factor, following the Canadian way, is 15 milligrams per day for food, but again I am just pulling that as a figure.

Thanks.

DR. ASKEW: Thank you. Dr. Ziment?

DR. ZIMENT: Well, I'm impressed by all these arguments, bringing down the dosage of ephedrine and I'd like to be responsible for making the ultimate suggestion, and that is the dose should be 10 to the minus 30 grams and sell it as a homeopathic remedy.

DR. ASKEW: Thank you. That gives the FDA a

range, which was what they asked us to come up with.

[Laughter.]

DR. ASKEW: We can probably adjourn now.

DR. KESSLER: We can end now.

DR. ASKEW: Yes. We're now ready to--except for possibly Dr. Blackburn who wants to make a statement, we're ready to begin our summary statements. Dr. Blackburn?

DR. BLACKBURN: I don't want to make a statement. I want to see whether if we vote for any of these levels, recommended levels that have come down 10-fold in 2 days, or in 10 months, down to 2 milligrams, what we're really doing, and I think only the people from the industry can tell us. Then if we know what we're doing, then we go ahead and do it. If we reduced it to those kind of doses with these kind of restrictions and this sort of quality control, is there going to be any market and are we banning the drug for use as a good supplement, in which case we might as well go and vote that way? I would like--

DR. ASKEW: Let's have Mr. Israelson respond to that.

MR. ISRAELSON: Thank you, Dr. Blackburn. I welcome the chance to offer a few perspectives. You're dealing with some of the scientific difficulties of this issue and we're dealing with the commercial difficulties of

this issue, and I think ideally we would like to achieve a safe dose that can be used widely by consumers in this country, at the same time enjoy industry compliance with many of the issues that had been raised here.

And I think that the sense that we have, in order to reach a scientific decision that has commercial reality attached to it--that the numbers that really seem to make sense to the industry would follow the Canadian experience because they have evaluated these issues, have established a dosage range which Ms. Ho advised us of, and she said to direct questions that they had very few reports of adverse reactions to that dosing range.

I'm very concerned that if the product is made unavailable that you'll drive it underground and then all of the concerns that you have about quality assurance will quite surely be a serious problem and that the legislation which was passed in 1994 gives us an opportunity to work with the agency and to work with you to establish some meaningful parameters. So just as a working suggestion, since everybody else has thrown theirs out, is that if we look at the Canadian levels, which were 6 to 8 milligrams 4 times daily, or 24 to 32 milligrams, without the addition of other stimulant materials and with good manufacturing practices, I think that that's something that the industry

would be able and willing to support and comply with. And in my judgment, that serves the broader public interest because you would actually have a significant change of commercial activity which would do a great deal to support your desire to protect public health and safety.

DR. ASKEW: Thank you, Mr. Israelson. We're going to--Dr. Harlander has a comment.

DR. HARLANDER: Is there a seven-day limit on that in the Canadian--

DR. WOOSLEY: But it says a drug, too. It's totally different.

MR. ISRAELSON: Well, you're drawing distinctions, and I appreciate the concern you have that they're using that as a traditional medicine. Now, is that a drug to you? But in the context of establishing numbers, safe ranges, and labeling practices, that's the problem that we have to deal with. Whether you choose to call it a drug or a dietary supplement, that's the reality that we have to face.

DR. WOOSLEY: But they're using it under supervision and that's not at all what we're talking about here. I think much of the discussion--

MR. ISRAELSON: No, no, no, they're not; no, they're not. It's a traditional medicine.

DR. CROOM: It's totally self-bought. There's no

supervision of this category in Canada. It's an OTC-type thing. You go in the store, you buy it.

DR. WOOSLEY: But what I'm saying is it's not labeled as a food supplement. That's the difference. It's not--

MR. ISRAELSON: Under DSHEA, we're able to have a lot of labeling that would essentially follow what the Canadian labeling would say, if that would be helpful to solve your concern.

DR. WOOSLEY: I'll save my comments.

DR. ASKEW: Dr. Applebaum has one final comment, and this is the last one before we start our poll.

DR. APPLEBAUM: And it's not even a comment; it's a very brief question. But, Dr. Inchiosa, I'm very concerned what you said earlier regarding the prolonged use even at low doses can result in myocardial necrosis.

DR. INCHIOSA: Yes, I--

DR. APPLEBAUM: But you only qualified it; you didn't quantify it. What is a low dose?

DR. INCHIOSA: Well, I was thinking of a dose even less than 10 milligrams per serving.

DR. APPLEBAUM: So it could include two?

DR. INCHIOSA: I don't know whether it could include two.

DR. APPLEBAUM: I mean, I'm asking. You raised it and we're talking about trying to ascertain a safe level.

DR. INCHIOSA: Yes. I think one can definitely--I mean, we had the extreme of the homeopathic dose suggested. One could certainly find a no-effect level, no toxic effect level, and then there will be no therapeutic level as well. But in ranges where you have a therapeutic effect, because you are optimizing catecholamine preservation, in many models that has been shown--in weight reduction regimens, patients have been identified on autopsy as having disseminated myocardial necrosis. So agents which release catecholamines, interfere with their clearance and metabolism, have the risk of causing myocardial necrosis.

DR. ASKEW: Thank you. Before we go into our poll, I want to explain just a little bit about the way the committee works. This is not a vote, as such. We like to stay away from the word "vote" because vote then implies some sort of binding resolution and we're a recommendation committee and we go on record with our views and that's what we're going to do.

Now, of the members of the committee, there are some that go on record officially and others that are not official polling members, so to speak. For example, Dr. Applebaum and Dr. Harlander are industry representatives and

are not--their record doesn't go officially on the record. We allow them to make their comment, but it is not on the record the same as the other members of the committee. Likewise, Mr. Ford, Mr. Israelson, and if Dr. Crawford had been there, would also be in that same category. We certainly allow them to express their opinion, though.

So right now what we're going to do is go around and poll everybody on the specific questions that have been posed by the Food Advisory Committee--I mean to the Food Advisory Committee by the FDA. After we've done that, then we'll go back and let everybody make a closing statement, and they can also say whether or not they approve the minutes of the working group that was held in October at that time. But we want to get on record separate and discreet and as fast as possible the answers to these four questions.

Now, you might choose to group questions 1 and 2 together, safe level and margin of safety, and answer it that way, and questions 3 and 4, no risk of significant harm and conditions that are associated with the risk of significant harm, together.

Dr. Woosley, you had a question?

DR. WOOSLEY: Yes, a clarification. I assumed that we would have a chance to express our opinions before a

vote. I still haven't really expressed my feelings on this.

DR. ASKEW: Let me ask Dr. Larsen. It was his suggestion that we do it in this order. I would certainly not be adverse to giving everybody a chance to express their opinion and then get to the vote. Dr. Larsen, how do you feel?

DR. LARSEN: I want to emphasize this isn't really a vote. You're getting a chance to get your opinion on the record, and the way I was suggesting that we do it is that we address the questions specifically first and then go to your general overall assessment, if you will, your summary statement. Now, if you'd rather go through the summary statement first and then--but I think what we want to do is make sure we get an answer to the questions that we have in the charge.

DR. WOOSLEY: I think it's usually better to get everybody's opinion and then derive the answers.

DR. LARSEN: Dr. Kessler?

DR. KESSLER: We just don't want to let you off the hook.

[Laughter.]

DR. KESSLER: I have promised a number of people that the agency will work hard to get to a decision soon after this advisory committee. Perhaps if there's, you

know, one or two general statements, sentences, first, that's certainly fine, but we really would like to go around and get the answers to these questions. Feel free to make some general, you know, opening, but we really would like on the first round for you to address the questions because we're just afraid you will never get there.

DR. ASKEW: If you would like to preface your specific answers to these questions with a preamble, go ahead, but you'll have time later to give a more detailed one, and I can certainly see the reason that you suggested it. But, yes, Mr. Ford?

MR. FORD: I just wanted to get clarification of the context of the question, Dr. Kessler. Were you asking people here if there is a safe level of ephedrine in terms of what they've learned today and yesterday, in terms of the literature that they're familiar with, in terms of the use of the product or products in their daily professional practice or--it's a pretty straight question that I would think would require some experience and expertise, so I'm just asking what the context of the question is.

DR. KESSLER: It's based on the record before individuals. We have a lot of different individuals with a lot of different expertise. We'll take that into account. For some, it'll be the information that has been presented

over the last two days. For some, it'll be information that has been presented both in the working group and over the last two days. For others, they certainly can draw upon the literature that they're familiar with and their own expertise, but it's the record before them as has been presented. I think that the starting base is over the last two days, certainly.

DR. ASKEW: Dr. Fukagawa has a flight that she has to catch and she was going to be first and I'd really like to give her an opportunity to speak before she leaves. Go ahead.

DR. FUKAGAWA: Thank you, and I guess I will be one breaking the recommendations that we go with our answers to the questions and a summary statement, since I'm combining both.

First of all, I would like to concur with the cautionary statements that were made by the working group and outlined in the minutes of the October 1995 meeting, in that I do believe that they have taken into consideration a significant number of the issues that have been raised over the past two days.

Now, to address the questions, regarding the safe level in dietary supplements, I must admit that I cannot separate out the supplements from the context of food and

will have to assume that most individuals, when they see something as a dietary supplement, may indeed infer from this that it can be taken safely on a daily basis. So knowing this and knowing the cautions that we've described in the working group minutes of 1995, I would concur with the Canadian experience in that the safe level in dietary supplements would be anywhere between zero to 3.1 milligrams per day of the ephedra alkaloids, and then one can make the calculations after that with respect to ephedrine in terms of per-serving and per-day recommendations.

With regard to the margin of safety and determining the safe level, I believe also that we can go with the homeopathic recommendations of Dr. Ziment of 10 to the minus 3 or 10 to the minus 4, up to the maximum of the 3.1 that I am recommending at the present time.

Finally, with respect to conditions, or question number 4, I don't think there are any conditions where there is no risk of significant harm when taken as a dietary supplement. And, finally, the conditions associated with risk of harm--I would concur that the issue of the pediatric population, the elderly population, those on drugs that may interact, especially in combination with caffeine and some of the other drugs that we heard about earlier, and conditions which would include pregnancy, heart diseases,

some of the psychiatric or psychotic illnesses that we're talked about, et cetera--and so therefore I think it's very difficult in making these recommendations independent of the kinds of health claims or claims that we've seen on the labeling of the packages that were before us over these past two days.

And I would seriously, on a broader point, concur with Dr. Clydesdale that it would be important for us to perhaps relook at the SHEA [sic] law, or I don't know what that--issue and consider that it might be appropriate to recommend that this be repealed. Thank you.

DR. ASKEW: Thank you, Dr. Fukagawa. Dr. Clydesdale has already given his and has left and we'll move on to Dr. Harlander.

DR. HARLANDER: As mentioned earlier, I'm not a voting member. I do appreciate the opportunity, however, to share at least my perception. I was not here the first day. However, I did receive the packet and had an opportunity to review it.

I do have some concerns that this is a drug masquerading as a food, and I share both of the last two speakers' concerns about DSHEA and feel that this is probably one of the first times we're going to be dealing with this issue if we keep that legislation the way it is.

I have some concerns about the difficulty in separating the claims that are made from the dosage and duration of use. If there is even an implication that this can be used for weight control, for energy, for a sense of euphoria, for bodybuilding, I think that consumers will not take into effect, even it's labeled, that it should be used for seven days because those are not things that we have concerns for only a week about. If we're taking something for weight control, we don't really even get much of an effect in seven days. So if there's an implied or an explicit claim being made, I have a real hard time separating that from the dosage and duration.

I also share concerns with other speakers about the lack of specifications, quality control, reliable assays, reliable dosages, and I know that the industry has made proposals for doing that and for putting those things in place and, to me, that would be a minimum of what needs to happen.

For those of us that are in the food industry, which I am, we are very concerned about specifications of any ingredient going into our products, as well as final specs, and we're dealing with biological systems. Food is a biological system. It's a natural product in many cases, at least in my business, and those kinds of specifications are

a minimum and quality control systems in place.

I have a real concern about the impact of the 11 to 20 other ingredients that are present in many of these products, and we've had discussions about the fact that we understand very little about those other alkaloids. The drug interactions have already been addressed by other people in this group as well.

I think that's my main--and a surveillance system. I think in the food industry we have 1-800 numbers. This might be a dramatic departure, but I'd like to see a 1-800 FDA so that these concerns go directly to the agency rather than to the individual companies on their own. I think that would be a responsible way for us to assess the true adverse reactions to these products.

I also had some concerns about--and it just came up very briefly about the traditional use of these products by the Chinese and the dosages that we're arriving from that based on that and then the fact that other drugs are used to counteract the effects of the ephedra. To me, that was new information to me and I have some real concerns about the need to really explore that more because if I'm taking this product, I probably don't have access to those other counteracting drugs at the same time.

So in answer to the questions, I don't feel

comfortable that we can come up with a safe level for a dietary supplement because I don't think people would use this just for seven days. We'd have to come up with a dosage that was going to be safe for long, chronic use because I think the kinds of things people would use these products for, they would not do them in short, you know, seven-day kinds of things. So therefore I think it's very difficult to determine a margin of safety, and personally I have a hard time coming up with a safe usage of these products where there is no risk of significant harm. Thank you.

DR. ASKEW: Thank you. Dr. Chassy?

DR. CHASSY: One thing that has become clear to me over the last couple of days is that we're witnessing perhaps the renaissance of traditional Chinese medicine, and I was very appreciative that Dennis Hsieh brought the book in and read a little bit out of it because I think it lends great guidance. They have thousands of years of experience with what is a medicine, not a dietary supplement. It is intended for use, whether by self-medication or prescribed by a practitioner who is familiar with it, for a short period of time for a specific therapeutic effect. And even that book told us of the dangers of side effects and adverse reactions and what to do about them, and as Susan just

pointed out, there were other herbs that were mixed to counteract some of the effects that one would expect from ephedra.

I think that it is disingenuous of the industry to wrap themselves in 5,000 years of scientific Chinese tradition in using these herbs and say that that tradition shows that these can be safely used because we are not using them under the same conditions, to the same extent, at the same levels and for the same purposes that their experience has proven them relatively safe in.

And that brings me to the second thing that the previous two comments focused on. We are talking about a dietary supplement which I as a consumer, when I walk into a store that sells these products, have every reason to believe are at least as safe as the foods in my diet that I mean them to supplement and so I would hold them up to a very high standard of expected safety.

In fact, there are people going into these stores and buying products because they believe, because they are natural and because they are herbals and botanicals, that they are, in fact, safer than the products that are offered over the counter or prescribed by the doctor, and certainly have no reason to believe that there could be adverse consequences.

I have a number of other comments I want to make later when we go around again, but those two things and the fact that we have very short-term and very low doses leading to adverse effects make me believe that it is impossible to set a total ephedrine or total ephedra alkaloid dose that is safe in a dietary supplement, and that would be my answers to questions 1a and 1b. I do not believe that there is, therefore, any margin of safety, although I believe that the proposals put forth by Dr. Croom and the calculations that Dr. Hsieh provided us with do give us guidance, should we want to adopt that position.

I believe Dr. Croom's proposal is at the very minimum what we would need to do to continue to have ephedra alkaloids in the marketplace, and I think Dr. Hsieh's experience in toxicology has guided us to a very reasonable number.

I can't obviously identify conditions for which there is no risk. That is a difficult question in any case because nothing is without risk, but in a food product or a dietary supplement to a food I have to have a very low level of risk. And finally, it is very clear to me at least that there is a risk in taking any of these products. There are people who are at greater risk when they take them, and they've been enumerated already for us. I'm particularly

concerned about people who are going to have preexisting conditions which have been noted, people who are going to exercise under severe physical stress. I'm concerned particularly about how they might perturb people who already have, you know, mental problems. There are a variety of people who I think should be steered away, but I think that can be dealt with in warning labels if they're sufficiently extensive.

DR. ASKEW: Thank you, Dr. Chassy. Dr. Benedict?

DR. BENEDICT: I will save my pithier comments until we go around a second time and just get through the questions as quickly as I can.

DR. ASKEW: Bless you.

DR. BENEDICT: Thank you. With respect to question number 1, can you identify a safe level, listening to the data, the lowest dose that we were told anyone was given was 1 to 5 milligrams, and under those circumstances there were adverse effects. Based on the data that we were presented with, I cannot identify a safe level because I never heard anybody say a level that was given that gave absolutely no adverse effects. So I cannot identify a safe level.

How would I determine a margin of safety in the face of that? If I were forced to do so, I would suggest

that we take the 10-percent rule and apply it to the lowest dose anybody has ever taken that gave an adverse effect, which would be 10 percent of 1 milligram, which would be 100 micrograms. But then you have to factor in the current status of the products, which seem to vary from up to 30-fold in the amount that they say they contain, and so you must divide that 100 micrograms by 30 to go down to whatever that works out to be, a small number.

Okay. Can I identify conditions for use under which there's no risk? I cannot because we've never heard a dose that did not cause an adverse effect when given at a dietary supplement; at least I didn't hear that. Can I identify conditions of use associated with a risk of significant harm? Yes. We've heard of two very unfortunate deaths that--at least two that were directly related to taking this substance as a dietary supplement, and so I can definitely identify such conditions.

DR. ASKEW: Thank you, Dr. Benedict. Dr. Applebaum?

DR. APPLEBAUM: Thank you, and I appreciate having the time to also answer the questions, realizing that because I represent industry, they will not necessarily be considered, and I'm going to follow Dr. Benedict's lead and answer the questions.

In regard to the first one, can I identify a safe level in dietary supplements for total ephedrine alkaloids, I think at some time in the future not only myself, but I think a committee will be able to identify a safe level. I think there is not enough data currently available for us to do that, and I say that for one reason, in particular. There hasn't been enough information provided to the committee today or yesterday to identify what the dietary supplement is. It depends on the manufacturer, it depends on the product. So there isn't--and I'm not comfortable at all in extrapolating from the therapeutic agent the pure compound to the dietary supplement. So in regard to 1a and 1b, no, I cannot identify a safe level. So, therefore, number 2 is moot because without a safe level, I can't identify a margin of safety.

In regard to question number 3, I think in listening to the experts, the physicians that compose this committee, there are conditions of use, but the use is under the supervision of an expert. I think we all at one time or another consider ourselves experts of ourselves and what we want and what we need, but in this case when you're dealing with an active pharmacologic agent, I think it's best taken under the supervision of a physician until the safety data are all in that can adequately define the dietary

supplement.

In answer to number 4, identifying conditions of use that are associated with a risk of harm, at this point in time there doesn't appear to be any conditions of use that are not associated with a risk of significant harm because there isn't enough information available to date on the dietary supplement to allow an adequate scientific safety assessment of the product. Thank you.

DR. ASKEW: Thank you, Dr. Applebaum. Dr. Blackburn?

DR. BLACKBURN: I'm not happy with saying anything on this. I would probably take the tack that--recommend that we take the tack that was used for olestra that it have a temporary approval and based on performance of the industry on quality control, change in promotion of these products and suggested uses and proper labeling, and so forth, we might reconsider it in a period of time.

I guess I am impressed with the concern about this going underground and I would like to see these issues being resolved, and since I think we're going to have a long-term relationship with new food additives of many sorts, I would like to see the quality of the science and the evaluation, as well as the industry performance, improved. So I would basically go along with Dr. Croom's suggested levels, with

required quality control; his suggestions for formulations, restrictions and final product; no promotion for muscle-building, euphoria, the conditions of risk; and review this again in a couple of years.

DR. ASKEW: Thank you, Dr. Blackburn. Dr. Jasinski?

DR. JASINSKI: Yes. Through a different set of reasoning, I come to almost the same dosages that Dr. Croom has. Assuming that there is going to be, because of vested interest from certain consumers who are going to want to continue to have this product, practitioners--there's a number of people who are going to want to have this, so picking a dose--my view is that you're probably going to wind up with a dose of no more than 40 to 60 milligrams of total ephedrine alkaloids per day.

The reason for this, just doing this and coming back again, from being a pharmacologist and a clinical psychopharmacologist and looking at this in terms of what we know about ephedrine, we know that from studies which have been done over the last couple of years that you can take anhydrous caffeine and give it to people and get amphetamine-, cocaine-like effects, maximizing at about 200 milligrams, between 100 and 200 milligrams.

These roughly wind up being at a level, at the

maximum, somewhere about 2.5 milligrams of amphetamine. 2.5 milligrams of amphetamine is equivalent to about 10 to 15 milligrams, 12.5 milligrams, of ephedrine. So one would look at this to keep it in this dose range of what people are using as the average or maximum sort of caffeine dose. You're talking about these sorts of levels of about 12.5 milligrams per unit sort of dose that would be the maximum of ephedrine.

Now, the difficulty is that we're not dealing strictly with ephedrine, so I haven't--it has been a long time since I took chemistry, so I can't calculate this back to the ephedrine base, but I would put this in terms of the ephedrine base. And because the other issue in this for me which is a critical one is that we're dealing with a preparation which has other ephedrine alkaloids in it, some of which we don't know whether they're similarly active or more active--but I think you only make the assumption that they're all going to be equally active to ephedrine, so I would take any ephedrine, alkaloid-base ephedrine, from the salts and put a maximum limitation that not to exceed that to be equivalent to 12.5 milligrams in unit dose in terms of this, which puts this in somewhere at 30 milligrams, and you could probably argue this up to 40 to 60, particularly in terms of--the other issue in terms of harm--I really don't

know how to judge the harm from this.

The fact is we have a long history of people using low doses of, quotes, "stimulants" chronically without any major consequences. There is data in the literature on the use of amphetamine-like drugs in cardiac patients, in cardiovascular patients which show that they don't enhance any toxicity of cardiac--so this is really a debate which is ongoing.

And whether these are effective in certain people with certain conditions and diseases, there is a literature on this, but we haven't seen any sort of review of the literature being brought to this particular discussion. Assuming that ephedrine is a stimulant with amphetamine-like characteristics, there's a tremendous literature on this and so I think there are certain things which you can glean from literature and principles which would particularly address this. There are classic situations in which you know you shouldn't take this, MAO inhibitors being one.

The other issue Dr. Inchiosa raised was about 10 milligrams of ephedrine. Yes, but that's intravenous ephedrine and there's a difficulty with that because if you give intravenous ephedrine, the intensity of the response is depending on how fast you inject it. For example, if you smoke a cigarette and you puff on it, you get a bollusk

hitting the brain very rapidly, so it's distribution in the brain which determines the effect. If you take it by the nicotine chewing gum where it comes in slowly, you can get the same dose level, but not get the same sort of buzz from it. So I just don't like to extrapolate from intravenous to an oral dose because sometimes it's not particularly appropriate.

DR. ASKEW: Thank you. Dr. Croom?

DR. CROOM: I hope this will help some because, yes, I would still say, only answering the question, to me it's very clear from even what I've heard in the last two days and even the creative marketing that I've seen done that I think you have to go--a low, but safe dose is 10 milligrams per dose, 8 milligrams ephedrine.

One reason I want to say that, whether we want to talk about--of course, all of us know it's an irrational place we're debating. We're talking about foods, we're talking about drugs, and botanicals don't have a home. They're still orphans, they're second-class citizens. So if we look at trying to preserve whatever wisdom is there from ancient use and science, I'm trying to say let's not kill whatever utility is there. Let's not debate it. Let's keep that there.

To preserve the safety takes GMPs, and my point is

I'm saying a certifiable GMP with a certifiable analytical method to raise the standards in this industry. Safety is definitely a concern with adding stimulant laxatives. We see xanthine alkaloids and MAO inhibitors. Those are ways to keep the product safe. That's what I'm trying to do, with some utility. It's obvious adverse events went up when the uses went to weight loss, energizer, muscle-building.

There have been a number of products for self-use, not Chinese traditional medicines, on this market--material, time and extent--in America; no adverse events. I'm sorry. There are good, safe products in these dose ranges that have been on the market a long time, never caused any problem. So I'm saying if the problems are starting because of misuse or whatever, then let's go ahead and limit it this time.

And I like Dr. Blackburn's kind of a temporary permit, in a way, actually, if you don't follow the rules, but I'd want the issue settled. Let me say that, that where you don't have a name, a label or a promotion for euphoria, energy, stimulant, weight loss, ergonomic, body-building or enhanced performance--let's face it; a weightlifter wants to lift five more pounds and taking something easy to lift five more. If I want to lose weight, I want to take more. These are things--for energy, also, I will tend to overdo.

Having a cold or a cough or asthma, or whatever

other reason I'm using this--even weight loss, if not overly promoted--maybe I can find a wise use without killing myself. That's why I'm trying to say limit those with our full warnings; tell the consumer as a dietary supplement what it's going to do to you physiologically. It's going to stimulate your heart, it's going to increase the central nervous system stimulation, it's going to raise your blood pressure. Don't mickey-mouse around, just tell them what it's going to do to them.

I would still say we do not have a material time and extent for long-term use, so I would still go with, whether it's 7 or 10 days--it doesn't matter to me, whether it's Buddhism or Christianity, how we set this, but a short-term exposure to this potent thing.

DR. ASKEW: Thank you, Dr. Croom. Dr. Bruner?

DR. BRUNER: Thank you very much. This has really been an education for me in terms of botanicals and an education for me in terms of the regulatory process. I would like to say that traditionally I looked at specific dosages of drugs that I used in practice based upon their effect because I knew what they were. I knew exactly what was in them, but what we're faced with is, as we say from other speakers, 11 to 20 different things in these particular items.

So I would really agree with Dr. Croom in what he has set as guidelines over the last two days, with the strict caveat that there be mechanisms to assure that what is contained in the item is actually that particular substance and in that particular quantity. I think that's critical to this whole issue, and also to say that in terms of having no risk, as we know, there are no absolutes in medicine. There are absolutely "no," "never"--we learn not to use that in answering multiple choice questions. Those were always the wrong questions, usually, and so I think in terms of labeling, there should be strict labels.

We as Americans tend to want things yesterday, and especially in looking at the weight loss field that is an industry that is so proselytized right now and quick fixes are the things. You know, you see advertisements, lose weight overnight; wear these special patches, you know, and you'll lose weight. And I think the claims are very germane to this and my question is really what is ephedra in terms of a dietary supplement if you remove all these claims. Why would any--I mean, it does cause some euphoric and some mood-elevating tendencies, but truly what is it?

Also, after that I'd like to add in terms of precautions, as we said, and strict labeling procedures certainly the issue of hypertension, of taking concomitant

drugs, of depression or psychiatric illness, of having glaucoma. We didn't mention that, and I think those things should be strictly adhered to, of course, in use in our pediatric population and use in our pregnant and lactating women. Thank you.

DR. ASKEW: Thank you, Dr. Bruner. Since time is getting short, I would just kind of ask people to really try and address the questions and then we'll get to you for your general statement at the end. Some people have planes to catch. We need to move rapidly.

Dr. Hui?

DR. HUI: Well, I would like to say that there is really no safe level for, you know, any substances, but now that we have to deal with this particular issue, we will have to come up with a number. Someone said zero and I think a reasonable number provided by Dr. Croom was 10 milligrams per dose. I think the safe level is always affected by concomitant diseases, physiological states, and also concomitant medicinals. And I think that it really needs to go down and I don't think that it should go to 1 milligram or lower than that, or even 3 milligrams, and that's why I was trying to shoot for a 2-milligram unit dose, assuming that some of the patients may take two, so that would be 4. Three times a day would be 12 milligrams

and I think that should be reasonably safe.

I mean, safety is really, you know, a difficult concept because what is safe for someone is not safe for another. What is safe for someone now may not be safe for someone at a different, you know, time point. So we just have to accept some risk if we assume that we are going to have this product, you know, available, and I think we need to have it made available because I don't want it to go underground and it would be even more disastrous and will be more difficult to control.

So in terms of the amount of ephedrine, you can do the appropriate calculation, but I would say that the total dose for a day will be 12 milligrams, and obviously some patients or some citizens may even go up on that. But I think that a unit dose of 2 will give us some, you know, leeway there, and also we can recommend that they titrate those because we take into account someone who is very sensitive. And if they are very sensitive, then they may get the result that they need, you know, with the 2 milligrams 3 times a day dose. So my lower dose, obviously, would be 6 milligrams, and I think the highest dose on label will be 12, but assuming that someone may even misuse it, abuse it, you know, it may go up, you know, to 24.

So in terms of conditions of use where there's no

risk--and I don't think that I can tell you any conditions because a lot of patients may not be aware of the risk factors that they have. So we assume that many of these patients or citizens will have these conditions, and then because many of them, as I said earlier, are under stress, taking other stimulants either knowingly or unknowingly and they really may be at risk. So I don't think there is any, you know, particular condition where there is no risk of significant harm.

And in terms of the kind of conditions that are associated with a risk of significant harm, I think that any condition that will be affected by enhanced adrenergic state would be at risk. Any drugs that may predispose the patient to have cardiac problems, to have CNS problems, psychic problems, and any drugs that the patient may be, you know, taking that will interact in some way either in a pharmacokinetic or pharmacodynamic manner should be listed. And I do not believe that we should allow the use of other substances in the preparation, and I also agree with the need to have good GMP.

I mean, we're suggesting a level that if we don't monitor it, then it doesn't mean anything. We already have to deal with the pharmacokinetic problem, you know, with the disposition characteristic of the patient or the subject, so

we need to at least get rid of one source of variability by having certifiable GMP.

And, finally, I think that it should be for short-term use. I have no particular date. You know, even three days--if someone is taking a preparation for a few days and they are, you know, not getting the benefit or they get side effects, they need to get medical evaluation. I mean, I would even suggest that the subject should be evaluation to be sure that they are safe to take, you know, this product, especially if it's going to be used in a higher dose.

DR. ASKEW: Thank you, Dr. Hui. I'm going to turn the Chair over to Dr. Chassy temporarily--I have to be out of the room for a moment--and just proceed with your reports. Dr. Fong, you can go next.

DR. FONG: Am I on? Can you hear me?

DR. YETLEY: Yes.

DR. FONG: Okay. Pharmacognosists don't necessarily always agree with each other. So, Ed, here we go again. Using the pharmacopeial requirement of the Japanese and the Chinese pharmacopeia of ephedrine alkaloid content in ephedra of .7 and .8 percent, not less than, and using the German commission E dosage of 1 to 6 grams per serving, I have surprisingly come to the dose of 7 milligrams, which isn't very much different, Ed, so I will

defer to your knowledge, so I will agree after all.

Not being a pharmacologist or physician, I would decline to answer question number 2--Fifth Amendment rights. In terms of question number 3, I have a serious problem with the last phrase, "of significant harm," "serious adverse effect in at least one individual." My daughter, who is 28 years old now, but as a child had great difficulty drinking milk--so milk is a food; milk presented serious effect to my daughter, as well as other Chinese or Orientals. Anyway, so from that perspective, I cannot answer that question either.

But for question number 4, certainly cardiac patients such as myself or people who want to use CNS stimulants or use it as street drug alternatives--those would certainly be conditions that should be precluded from use. So, that's all I wanted to say at this moment.

DR. CHASSY: Dr. Yetley?

DR. YETLEY: Could I ask for a point of clarification? When you said 7 milligrams per day, was that per day or per serving, and was that total alkaloids or--

DR. FONG: It's per serving, total.

DR. YETLEY: Per serving?

DR. FONG: Right. Total alkaloid, and if one used the effect that alkaloid content, ephedrine content, varied from 50 to 90 percent of total alkaloid being ephedrine,

then you can extrapolate 90 percent, so go down to 6 milligrams as ephedrine.

DR. CHASSY: I'd like to ask everybody to please try, as we just heard, to specifically address each of the four questions as part of your overall response. Dr. Dentali?

DR. DENTALI: Thank you. As it's difficult to separate in my mind the alkaloid from the plant, it's difficult for me to separate the answers to these questions from another view. So in the interest of complying with your request and in time, I'd like to agree with the comments--and I have very little to add, actually--of those presented by Blackburn, Croom and Jasinski.

DR. CHASSY: Dr. Ricaurte?

DR. RICAURTE: Well, it's going to be tough to beat that for brevity. With regard to the issue of identifying a safety level, the answer is I can't, for two reasons. I think it's telling that just from October '95 until here we are 8, 9, 10 months later, we've already gone from an estimated safety level down 10-fold, and I'm not quite sure on what basis we're doing that.

There is uncertainty as far as I'm concerned on the available data with regard to the ephedrine alkaloids themselves to, with any certainty, say here is a safe level.

You compound that with the fact that, as the question is phrased--and I think it has been very carefully phrased--it's not only a question of the amount of ephedrine alkaloid, but in a dietary supplement it just compounds the problem.

We've heard about the problems of quality and quantity control, and so given the uncertainty about the pharmacology of the ephedrine alkaloids themselves, the combinations and the vehicle that they're being delivered in, I just can't see how in the world we can arrive at a safe level.

With the issue of a margin of safety, I'm left at somewhat of a loss because for a margin of safety you really have to have some indication and what I've heard this afternoon is that all the purported purposes of use are being taken off the table and it leaves you with, well, what the heck are we going to use this for. If there's no clear answer to that, then the margin of safety, quite frankly, has to go to infinity because you can't do a risk/benefit when we don't have a perceived benefit.

Question number 3 is--I'm not sure that there's many compounds that can satisfy that requirement, so the answer is, no, I can't, but I'm not sure that it's entirely a fair question with regard to the ephedra alkaloid per se.

Question number 4, conditions where it creates problems--obviously, high doses, more frequent doses, predisposed conditions, sensitized individuals, and just use of these compounds in unsupervised settings--I think there's agreement on that. So those would be the answers to the four questions I have.

DR. CHASSY: If anybody who hasn't spoken or any panelist who has spoken needs to go out or to check out or to leave, please feel free to do that. We're going to continue on and not take a break. Is there anybody else who will need to speak that has an imminent departure schedule?

[No response.]

DR. CHASSY: Okay, then let's go back to Mr. Israelson.

MR. ISRAELSON: Thank you. With regard to the questions, I'm still concerned that some of the crucial cases on which some of the opinions are being formed here at the low dose is we simply don't have adequate information. We understand from Dr. Love that these are combination products and we haven't had a chance to review what the composition or the potency of those products are. So with that reservation that we're making decisions based on crucial cases without adequate evidence, I would repeat that the Canadian proposal as it's being used there is a

reasonable model to follow. And my understanding of that proposal is it would be based on 6 to 8 milligrams of total alkaloids. That would give a daily value of 28 to 32 total alkaloids. Ephedrine would be approximately 20 percent less than that for calculation purposes.

I don't feel qualified to comment on point 2, for medical and scientific reasons, and I agree with Dr. Ricaurte that question 3 begs the question. I'm not certain that there are any substances really in the food supply that may not meet that problem.

DR. KESSLER: Can I just help so we don't get off the track on milk, please? Significant risk--MIs, seizures, death--I don't think the food supply has those kinds of products.

DR. FONG: You have drugs, erythromycin, milk, dairy product interactions, stuff like that.

DR. LARSEN: On the microphone; we're not getting you on the microphone.

DR. KESSLER: Again, I would ask you not to trivialize some of the serious adverse reactions. So when you see "significant risk," we're talking about significant risk.

DR. RICAURTE: With that qualification, again, I'd probably have to pass on 3 and 4 with respect to the

scientific issues.

DR. CHASSY: Mr. Ford?

MR. FORD: Well, based on the information that has been presented the last two days, I have to give a programmed answer because I think it's, under the circumstances, a programmed question. We are not able to apparently, in the context of this meeting, identify a safe level. I'm not a physician or a scientist, so I can't use it from the base of my experience.

I did want to ask Dr. Bruner a question, but I'll ask her when she comes back because I can understand the urgency that anyone would have. I am familiar with the Canadian experience, and what I wanted to ask Dr. Bruner about was her experience with the ephedrine in her diet program if it was ephedrine combined with caffeine because a notable change from the current product formulation that Dr. Croom's recommendation obviously implies is an absence of caffeine or any other products, any stimulating products, or any other products, period, right, Dr. Croom?

DR. CROOM: Yes. My recommendation is no xanthine alkaloids.

MR. FORD: Right.

DR. CROOM: And I don't think the Canadian product has xanthine alkaloids, is my understanding.

MR. FORD: No, I don't think it does.

DR. CROOM: I'd like clarification, but I'm--

MR. FORD: So since I don't feel in a position to answer the questions, a bottom line is Dr. Croom's suggestion, because of his expertise, I believe the industry could support.

DR. CHASSY: Dr. Woosley?

DR. WOOSLEY: Can I identify a safe level in dietary supplements for total ephedrine alkaloids? I have to step back and say there's no ephedrine in my diet and why would I want to supplement my diet with something that I know as a cardiologist and a pharmacologist has acute toxicity that can kill and chronic toxicity that can cause chronic myocardial necrosis?

So I would say that there is no safe dose of ephedrine when used for weight loss, energy, or any other of the currently popular reasons because of the variability in the human response, the variability in the products that are now available, and the potential for increasing the dose in the non-monitored use that is taking place in the dietary supplement situation.

What margin of safety should be used in determining such a safe level? Again, I can't identify such a safe dose. There are no data, as someone pointed out

earlier, with doses that are safe. All the doses that have ever been administered to man have documented serious toxicity.

Can you identify conditions for use of ephedrine alkaloid-containing supplements under which there's no risk? I cannot because there are people that we know will have increased risk, but are unaware of that risk, people who have undiagnosed hypertension, people who have barryaneurisms of the blood vessels in their brain that will pop when they have an increase in blood pressure after they take a dose of ephedrine. There are people with hyperthyroidism that don't know it and will be taking drugs to make them feel better and stronger. So, no, I cannot.

DR. CHASSY: Thank you.

DR. WOOSLEY: The last question: Can you identify conditions for use where there is associated risk of significant harm? Yes, I think we can--pregnancy; women; children; elderly; weight loss; people who are on diuretics, other drugs. It is the entire population, frankly, and I think one of the things I would close with is that these people are taking these drugs for exercise performance enhancement in many cases, whereas the available data indicates that when you do so, you actually have a perceived improvement in performance and not a real improvement in

performance.

DR. CHASSY: Thank you. Dr. Inchiosa?

DR. INCHIOSA: Yes. Regarding the first question, I think the key is can you identify a safe level in dietary supplements, and I cannot identify a safe level for a dietary supplement. And I think the problem of that, the dilemma it produces are the parts of the recommendations which I know are well-intentioned, but there's no value claimed. So now we have eliminated all of that and I could imagine this is going to be very confusing for the consumer, who now looks at a product that claims nothing, yet has a tremendous list of warnings because the warnings are going to be increased.

And so, really, in an age where we're trying to increase information it's disinformation or no information or only a condition of more confusion. So, therefore, I cannot identify a safe level for dietary supplementation. I have already talked before and I will later about therapeutic, but I'll go on. So, therefore, I agree with Dr. Ricaurte that since you have no claimed benefit, there's no margin of safety that can be calculated.

In terms of conditions for use of these materials where there would no risk, it would be at a no-effect level, the homeopathic dose, but that would be fraud to the public.

You'd be defrauding the public and maybe when we get to extremely low levels, it's approaching that, and any even benefit for the herbologists that they feel might be resident in these materials is not going to be realized. So I don't think very low levels or vanishingly small levels are going to avoid either any concerns about people going underground for it. So, no, I don't think you can.

And Dr. Woosley said many of the concerns. I think high dose--in terms of risk of significant harm, high doses, combinations with caffeine and other stimulants, in combination with exercise because of adrenergic stimulation, and all those many risk factors which Dr. Woosley indicated would be increasing the risk of harm.

DR. CHASSY: Thank you. Dr. Marangell?

DR. MARANGELL: Yes. Regarding a safe level, at this point based on what has been presented and considering serious adverse events and not side effects like insomnia which are expected, I can't currently tell you that there is a safe level. I'm concerned about extrapolating from traditional Chinese practices. I'm concerned about extrapolating from the pharmaceutical. I'm concerned about the variability in the botanical products. I'm concerned that I at least haven't seen data that there's going to be a reliable assay to measure whatever level it is that we set.

I am also concerned at the serious adverse events in the 1- to 5-milligram range. I know we don't have a lot of data on that, and perhaps for many people that's fine, but I also realize that individual variation is going to play as much of a role as a particular dose level is. It may be possible to come back and readdress this issue with pharmacokinetic studies, with better assays with single products, as opposed to the combination products that are on the market now. But with what we've got, I don't think that this is safe as a dietary supplement and I do believe that both consumers and physicians believe that if something is sold as a dietary supplement or as a food that it is safe for general consumption, and I don't believe that to be the case with these products.

Margin of safety--as the others, I can't comment on that. Number 3, no, and number 4, similar to others, certainly there are conditions that increase risk and I think that this is to a substantial portion of the population, not a small minority that has an allergic reaction to milk or shellfish. I really think it's a different type of scenario.

DR. CHASSY: Thank you. Dr. Ziment?

DR. ZIMENT: This is only two days in a long career that I've spent discussing herbs, which is perhaps a

shame. Maybe doctors, physicians in regular practice should know more about herbs and maybe the FDA has a big responsibility here to educate physicians about herbs, and also about the use of the alternative drugs in orthodox medicine because I feel a lot of physicians don't know how to prescribe ephedrine after hearing yesterday's discussions. I sincerely hope the FDA will invite me back if you ever discuss garlic, or I wouldn't mind ginseng and ginkgo. I think they're good ones to discuss.

The real problem, I think, that we face is the misinformation out there. If the ordinary physician or the lay public try to learn about herbs, they can read about these things in books which give anecdotes, misinformation, non-facts, imaginary facts, and a smattering of pseudo-science. And by and large, the information is outrageously bad and the products that are sold are mislabeled in a quite outrageous way, also.

So I'm strongly in favor of doing something to prevent this and I think one of the best ways we can do it is ensure that if people choose to buy herbal products, they can recognize that they are not getting real drugs in real dosages; they're getting alternatives to real drugs, which implies a bit of magic, and the doses will be much less than in the real drugs and maybe the magic will act

synergistically to achieve the objective that the patient wants.

So my recommendation is that ephedrine, as such, has always been prescribed by orthodox physicians in a dose of about--a minimal dose of 15 milligrams 3 times a day for adults and proportionately less for children. That should be the baseline dose for the orthodox, and I believe it's safe even if used for a prolonged period of time because I certainly used it that way. I've looked at the literature and I don't see much evidence that that dosage is harmful.

The next issue is to go back to the real question, one, can you identify a safe level? I don't think that's a fair question. Maybe the question should be can you identify a reasonably safe level, and that's where I would say in a dietary supplement the dosage should be substantially less than the level that one would use for an orthodox prescription. Therefore, my recommendation for ephedrine, per serving, would be not more than 5 milligrams, and therefore not more than 15 milligrams a day, and I think that would make 6 milligrams total ephedrine alkaloids per dose or serving and 18 milligrams per day.

We have heard today that the larger doses which have been recommended are dangerous and I guess some people think the homeopathic dosages are fraudulent, and so I'd

like to make a suggestion to the drug industry. We've heard a lot about allopathic doses. We've not discussed homeopathic doses and I'd like to suggest a range in between which we might call hollopathic dosages and that would certainly suit the new age people who might want to take these drugs. And I would recommend that the dosage for ma huang should be related to the new age thinking and should be 0.365 milligrams given not more than 7 times a day for not more than 28 to 31 doses for not more than 7 days of time and maybe one extra dose on the birthday and further dosing should be discussed with one's astrologer.

[Laughter.]

DR. ZIMENT: I really feel people are using these drugs in that type of fashion, and therefore one should make sure they're not given an opportunity to use dietary supplement as a substitute for real drugs.

Yesterday, Dr. Jones suggested maybe we should warn people that over-use of this drug would cause impotency. I think that would be a sexist thing to do, since mainly women are using the drug, and I think maybe what we should warn people is--and maybe actually do this--instead of combining the drug with a laxative, combine it with Ipecac so if they take too much, they'll just vomit it and that might prevent them from getting an overdose.

I think the FDA really does have a great opportunity here to educate people and to help us get over even some of the misinformation that we might have expressed today. For instance, I don't believe there's much evidence that it's harmful in pregnancy. And, in fact, for a long time asthma specialists were advising that asthma be treated with ephedrine in pregnancy because it had so many years of proof as being a safe drug. So I think there's a lot of information and disinformation and misunderstanding, and I think the FDA could do a lot to put together a real understanding based upon a correct analysis of the literature and present it both to orthodox practitioners and to the population in general.

DR. CHASSY: Dr. Askew is going to step out of turn here.

DR. ASKEW: I have a plane to catch, also, and I may stick Dr. Chassy with finishing up this meeting. It has certainly been enjoyable and enlightening for me, and I must say I agree with Dr. Ziment that I would probably rather be considering some other herb, such as garlic. I do think that herbal supplements are very interesting and perhaps are appropriate, but this particular supplement is somewhat--and the questions that have been posed are somewhat like asking a convicted criminal if they're rather be shot or hung, the

way that we have to answer this. But we're supposed to give a direct answer and that's what I will try to do here and that's what I've been encouraging you to do.

From the information that has been presented to me, I've been impressed by the amount of people that are actually consuming this product without having adverse reactions, and I draw more my conclusions as to its relative safety from that than from the adverse incidence reports which are very difficult to deal with because of the nature of the reports.

I think I will follow the suggestions of Dr. Croom, roughly, of 10 milligrams total ephedrine alkaloids per day. Something like 2 milligrams per dose would seem reasonable and calculate the total ephedrine from that. Margin of safety--I think that 20 milligrams per day would be an upper level that shouldn't be exceeded.

As far as identifying conditions where there would be no risk of significant harm, when it's asked in that manner, I cannot really identify any condition in which there would be no risk of significant harm. I do think there's particular risk of significant harm when these products are used and promoted as alternatives to psychoactive drugs for young, impressionable teenagers and adults. And when they are presented in that manner, I think

there is risk for significant harm because they will be abused under those circumstances. Thank you.

DR. CHASSY: Dr. Wang?

DR. WANG: Thank you. Again, it is rather difficult to answer the question, can you define a safe level in dietary supplements. Again, it's dietary supplements that we are learning that have caused adverse events, or combination products with various amounts of other stimulants or other types of ingredients. So, again, in order to answer that question, I will go ahead and use the same level that I earlier proposed that if OTC drugs allow the use of ephedrine, which is the synthetic component, I will extrapolate that and say that for total ephedrine alkaloids per serving would be 5 milligrams per serving, and that would be 15 milligrams per day.

And, again, the ephedrine level--again, I'm assuming the botanical source to contain 50 percent ephedrine, 50 percent of the other alkaloids, so I would give it a per-serving of ephedrine to be 2.5 and, per day, 7.5. What margin of safety? What I did is just took a 10-fold safety factor from the OTC maximum level per day basis for, again, ephedrine alkaloid.

Again, can you identify conditions of use of ephedrine alkaloid-containing dietary supplements under

which there is no risk of significant harm? Again, I'm thinking along the line of natural-occurring ma huang, raw herb in its raw form, stems, under the supervision of a health care provider.

Number 4, can I identify conditions of use that are associated with a risk of significant harm? Yes. As my colleagues here have pointed out, there are a lot of them, especially when you have the uses are not traditional ways of using it as a medicinal use. Thank you.

DR. CHASSY: Thank you. Dr. Potter?

DR. POTTER: Thank you. I don't think the general public distinguishes between food and dietary supplements. The assumptions that go into the rather casual way people make food choices in view of the poorly predictable, almost idiosyncratic adverse reactions to a range of doses makes me reluctant to identify a safe dose based on current data.

Using the traditional risk avoidance strategy expressed by Dr. Hsieh, I think a tolerable level of risk might be identified particularly if better data were available for low-dose effects in people who have high-density receptors.

I think in terms of question number 3, conditions of use for no risk of significant harm, I think that we heard a lot during the last two days of specific therapeutic

indications for ephedrine under which the drug has been used safely and I think that within that therapeutic realm, a safe use can be defined. In terms of question number 4, I think Dr. Woosley has characterized most of the highest risk conditions, although I think Dr. Askew also, in addition, identified that highest risk category for abuse.

DR. CHASSY: Thank you. Dr. Guzewich?

MR. GUZEWICH: Thank you. In keeping with the request that was made earlier by Dr. Askew, I will not--I have several other comments I would like to perform and since I've switched from a 3:00 p.m. plane to a 9:00 p.m. that tends to leave at 10:00 or 11:00 at night and will be home at 1:00 or 2:00 in the morning, I've got lots of time, folks, so you'll sit and hear me out eventually, until they turn the lights off.

[Laughter.]

MR. GUZEWICH: So answering the questions that I was asked to answer, as a food regulator I cannot, in good conscience, identify a safe level of ephedrine in dietary supplements, which I think of as foods, question number 1. Question number 2, the margin of safety--I would use the kind we use in food additives, which are like a hundred times below the no-effect level kind of thing, and since I don't think there's a no-effect level demonstrated here,

it's down to the homeopathic status.

Question number 3, conditions of use under which there is no risk--I agree with Dr. Woosley and others who have commented on the fact that I don't think that that exists based on the information from the experts I've heard here.

Can I identify conditions that are associated with significant risk? Well, given the fact the Chinese have this long experience and use it under very controlled substances [sic], and like Dr. Ricaurte and some of the others have said about, you know, high dose, exposure to other compounds, underlying health conditions--if the CDC has a figure, you know, for infectious disease, which is my area, food-borne disease, that 20 to 30 percent of our population today is at risk for food-borne disease from infectious sources for high-risk population, I don't know if that is a fair number to say for these kind of compounds.

But if you went through and identified all these various factors we've spoken about today, you'd have a surprisingly high percentage of our population that fits into some kind of a category. And given the fact that many of these effects that were described by some of our experts here are conditions that people don't even know they have, it's difficult for me to be any more precise than that on

that question.

DR. CHASSY: Ms. Richardson?

MS. RICHARDSON: Number 1, I would say no at this time. At this time, I have not seen any evidence that would indicate that there's a safe level in dietary supplements. Also, that goes for a and b. However, I would say that the FDA should probably look at the suggestions from Dr. Hsieh and Dr. Croom as they are looking at safe levels.

Number 2, no again. Number 3, with regard to dietary supplements, the answer is no, but certainly Dr. Bruner has talked about her use of ephedrine for therapeutic uses and Dr. Hsieh and Dr. Hui have indicated that as well. Number 4, certainly all of the conditions have been listed by my colleagues, but I also found it interesting that Dr. Jones in his testimony also indicated that people who are taking tyramine-containing foods such as cheese, liver, red wine, might also have to exercise some caution if they are taking ephedra.

I would also stress that the baby-boomers are taking over. It is an aging population. According to Time Magazine and everything else, we are all overweight and everyone is seeking to get thin, so the entire population would, I think, be interested in dietary supplements that are a euphemism for weight reduction.

I am concerned that when you look at post-menopausal women who are at high risk for heart disease and for African Americans for whom hypertension is a serious issue--and it is called the silent killer--that they would definitely be at risk of taking a dietary supplement that contains ephedra.

DR. CHASSY: Thank you. Dr. Katz?

DR. KATZ: Thank you. When I looked at this question, I had to divorce my experience as a physician with ephedrine since as a practicing pediatric pulmonologist back in the late '70s and early '80s we used a lot of ephedrine for children with asthma. It has been supplanted by obviously much better drugs, but we saw very few serious adverse effects.

But the question here is not to use the drug in that setting. The key thing is to define whether it's safe in the context of a supplement to a diet or a dietary supplement and that, to me, has a lot of implications. One is that it becomes widely available to the general population and, in effect, there's no regulation of its use. Despite all the label warnings we can put on it, people are going to use it however they feel like using it and that, to me, changes the standard completely.

And I would agree with one of the earlier

commenters that, in effect, this is a drug that is being masked as a dietary supplement. And based on my two days of being here and reading all the literature, to answer the four questions, I really cannot identify a safe level of ephedra alkaloids in dietary supplements, for all the reasons that were mentioned before.

And just in looking at the serious adverse events, it seemed to me that there were serious adverse events even at the lower range of doses, and that I find quite disturbing. So the answer to number 2 is obviously there is no margin of safety, since I can't define number 1. And number 3, yes, I think there are conditions that ephedrine alkaloid-containing drugs can be used under a physician's or other health care practitioner's guidance, but certainly not as a dietary supplement. And the answer to number 4 is I think there are multiple conditions that are associated with the use of significant harm and I think they have been mentioned by the previous speakers. Thank you.

DR. CHASSY: Thank you very much, and finally Dr. Hsieh.

DR. HSIEH: For those who are in the area of environmental toxicology, it is a common practice to estimate the safe level of a chemical in an environmental medium, including dietary supplements, based on very limited

data. We do that all the time, and based on the toxicological principle of the dose makes the poison, there's always a threshold dose, namely a safe level for a chemical, including ephedrine or ephedrine alkaloids, and this will be my position. My position as an environmental toxicologist--I say that there is a safe level of these compounds in the dietary supplement, however low a level it is.

And there are very well-documented federal guidelines to do this kind of estimation and the methods were already outlined by me earlier and by using those federal document methodologies and making reasonable assumptions. So if the methods and the assumptions are reasonable, then my answer to question number 1 would be that the safe level for ephedrine is 2 milligrams per person per day. It's not per serving; it is 2 milligrams per person per day for a limited use because the assumption made for that is for lifetime usage. And the total ephedrine alkaloids safe level--I used the same figure in consideration of the possible synergistic effect of the different alkaloids even though the individual constituents may be lower in potency than the ephedrine.

And question number 2, the margin of safety that I used--if you take the data from animal LD-50 as a starting

point, then my margin of safety is 10 to the minus 4, and if you use the human experience in Chinese medicine, then my margin of safety is 10 to the minus 2.

Question number 3, can you identify conditions of use for ephedrine alkaloid-containing dietary supplements under which there is no risk of significant harm? The answer is yes. Based on my approach, the conditions of use--if you limit your dose not to exceed 2 milligrams per day per average adult person and if the assumptions and the methods that are used for this estimation are reasonable, then that would be the conditions of no risk of significant harm.

Question number 4, the conditions of use that are associated with a risk of significant harm. The answer is yes, and the level is 20 milligrams, 10 times more than the no-risk level. If a person takes this compound more than 20 milligrams per day, then the likelihood of having risk of significant harm is there.

And one point of clarification with Dr. Yetley. In question number 1, you are asking us to come up with the safe level of the compounds, but the product in question is the ephedra or the herb. So I assume that you are using these compounds as a surrogate to estimate the presence or the content of ma huang in the product. Is my assumption

correct?

DR. YETLEY: Any considerations we would have would be relative to the content of ephedrine alkaloids and we wouldn't deal with it in a regulatory manner from the amount of ma huang. We would deal with it in a regulatory manner from the content of ephedrine alkaloids, regardless of the source. There are other botanicals, also, that could provide those.

DR. HSIEH: I thought based on our discussion in the last two days we are not to equate the herb with the alkaloids.

DR. YETLEY: Talking about the ephedrine alkaloids as a unit that we're focusing on, that's right, but you have to take into account the various sources, also, in your background information, but we are focusing on the level of ephedrine alkaloids. Now, you could back-calculate from that to the amount of ma huang or whatever source they use.

DR. HSIEH: Right, that is my assumption. So you are, in fact, using the alkaloids as a surrogate--

DR. YETLEY: That's right.

DR. HSIEH: --to calculate the content of ma huang in the product.

DR. YETLEY: That's right.

DR. CHASSY: We've finished the first round. I

think everybody has answered the four questions and we're now going to go around and let people make more general comments, summarize their positions, starting with Dr. Harlander.

DR. HARLANDER: I made all my comments previously. Thank you.

DR. CHASSY: Dr. Larsen tells me, as Chair, I have to wait until the end to make my comments, so, Dr. Benedict.

DR. BENEDICT: I respect that we should keep the substance available for medical practitioners of whatever stripe they happen to be. I do not wish to interfere with Chinese herbal medicine practitioners or acupuncturists or anyone else. However, I don't really want to leave here with the death or disability of another young person on my conscience and I'm having serious difficulty with this concept. And having raised two, I know that the young people of this country are intelligent, they're well-informed, they're very respectable people, but there's a subgroup of young people who are highly adventuresome, who are highly rebellious, and this subgroup is going to abuse ephedra regardless of labels, regardless of warnings

And the cat, frankly, is already out of the bag. We can remove all of the labels regarding weight loss and all of the other things and people are still going to know

that this is something that they think will work. Many young people already abuse drugs, abuse steroids, and these are highly warned against. I think that we have to protect the young people until they are sufficiently wise and sufficiently mature to protect themselves, and for this reason I just really have a hard time formulating this substance as it's being sold today.

I do not think the product should be available to anybody under the age of 21 years old, period. If they need it as a drug, they should get as the hydrochloride from a physician. I think the product should never be formulated with synergistic agents like caffeine, as has already been said. I think that if we allow it to be formulated, we must also include warnings against dietary caffeine and xanthine alkaloids and all of the other things that people have already mentioned.

I have a hard time even making it available as tablets, capsules, reduced extract because a committed young person who wishes to use it improperly need only go to any of those three and they can misuse it indiscriminately. I just have a hard time with that. If we want to allow it to be used for weight loss--we have the Danish study, we have a physician to my left who have been using it for weight loss--why not put it under the care of a physician and have it

regulated properly?

And finally--or not finally--almost finally, I think the ephedrine alkaloids represent an imminent hazard as they are currently formulated of both a large number of adverse effects and a serious adverse effect in at least one individual, and I urge the FDA to consider this in their deliberations.

And the final comment that I have is with respect to DSHEA. This is not meant to be totally amusing, but it reminds me of bicyclists on the campus of the University of Kansas. DSHEA allows people to ride on the road as a food or as a vehicle and then, when they come to a crosswalk, to quickly become a pedestrian on their bicycle and go across that crosswalk irrespective of the traffic light. It's a middle ground that is unregulable, and I know that it's a law and I know we have to deal with it, but I would like this to be reconsidered, if possible. Thank you.

DR. CHASSY: Thank you. Dr. Applebaum?

DR. APPLEBAUM: Because of time, I think my views have already been very well articulated, so I won't take up any more time, except to say that there have been terms such as "patients" and "subjects" used today in determining what the safe level of ephedrine should be, or the safe level, I should say, of dietary supplements containing ephedrine and

ephedra alkaloids. I just want to remind the committee that we're talking about consumers, and in terms of dietary supplements we're talking about food. Thank you.

DR. CHASSY: Thank you. Dr. Jasinski?

DR. JASINSKI: Yes. I have just a couple of points, just sort of--Dr. Guzewich, listening to him, and making some points. One is a time to be critical both of the FDA and the industry and looking at this of what's in the public interest. I think it's quite obvious in terms of anything that we do as regulators recommending regulation, you're going to do very little, and that's just from a cynical viewpoint of looking at people and behavior, consuming substances and getting appetites that can affect appetites and establish repetitive behavior, whether it be cigarettes or whether it be caffeine, whether it be alcoholic beverages. We can do very little to change behavior and we have a whole history of warnings on cigarettes and why cigarettes are bad, and people don't change their particular behavior.

In my estimation, listening to these massive number of doses, you've created a group of consumers who already know information and they don't get their information from what the FDA says and the package inserts. They get it from their peers and the underground sort of

group who gives them the information which is going to say that ephedrine alkaloids give you increased energy, help you with all of these sorts of things and these claims.

Secondly, I have been disturbed to some extent by what is really the lack of either scientific scholarship or scientific quality through all of this. I mean, that's just my personal particular belief. I think that this is something--not to be particularly critical, but it's like the question I asked Dr. Love in terms of did she write a report, was it reviewed, was it peer reviewed, making this available, before you start getting into these discussions.

Thirdly, I think there is a telling point which was made that you have to be very cautious. I have been both historically and been involved in people that have made decisions that have driven things underground. I think what amazed me is watching the antibolic steroids of people passing laws because they got concerned about athletes using these. We have now a whole underground economy with antibolic steroids being imported which are being used which are less pure than those which were manufactured as pharmaceuticals coming in, and that's creating public health problems and uncertainties.

And I suspect that people are right and I think that this is--the other thing that is particularly

disturbing is that in terms of behavior I would encourage both the FDA and the industry to reduce this adversarial sort of issue we've had here because we've had, you know, mostly the adversarial sort of people taking data and pushing this up. And I would think it would be better to encourage industry to come in with a position which they can defend on what they're going to do voluntarily and that this would be legitimate to set the standards. It would be much better than trying to impose a policy. That's just my own personal sort of philosophy that this would be much better. Beyond that, that's all I have to say.

DR. CHASSY: Thank you. Dr. Croom?

DR. CROOM: I'd just like to thank everybody for their indulgence. I'd like to thank everybody for what's a difficult job and hope that we can come together to look at these benefits, and I would reinforce one thing. It's not clear and there are a lot of paradigms here. We've got to find a better way, I would say, to come together and talk about how do we impact the public health because there are benefits coming here and not just risk, and we've yet to sit at the same table and do that as one people and we do need to look at the public health impact of how humanity has decided through the ages to use plants for their health. This has never, ever been handled as a public health issue

in the history of humanity. A drug discovery issue, yes; a public health issue, no.

DR. CHASSY: Thank you.

DR. JASINSKI: Can I just make one quick point?

DR. CHASSY: Go ahead.

DR. JASINSKI: I think there's another responsibility of the FDA, and that is consumers are buying this stuff assuming it's the same it's the same way they buy food products. FDA has provided an imprimatur on the quality, and I think it's very important that the FDA inform the public for an informed consumer that they are not responsible and that they are not responsible, nor are there any regulations for quality control which are regulated, not like you say for meat or food or even the manufacture of beer where there are standards. And I think that's an important thing they have to do to make this known that they do not have this responsibility and that a consumer, when he buys this, is accepting a risk from an unregulated product.

DR. CHASSY: Thank you. Dr. Bruner, there was one question that came up while you were out of the room.

DR. BRUNER: Yes, my imminent departure, yes. Caffeine?

DR. CHASSY: That was specifically whether you used caffeine and/or aspirin with the ephedra therapy.

DR. BRUNER: Mr. Ford, I know that was your question. In terms of our--what we do in the informed consent in using ephedrine, I stipulate people, because this is a sympathomimetic--well, because it does cause increase in heart rate and other sympathetic systems, that they are to limit their caffeine use to one cup a day or one diet soda a day. I stipulate, because part of the side effects may be stimulatory in nature, to let us know, and certainly that caffeine or other xanthine alkaloids, other substances in that particular instance, do accentuate it. And most of the data that we look at in obesity literature uses dosages far greater than that at 100 or even 200, 300 milligrams. So, that's what we do.

MR. FORD: Okay, so you don't use it specifically in combination? You don't use it combination products?

DR. BRUNER: No, I don't, or with aspirin, no. I use it singularly.

MR. FORD: And did you make that decision based on--I'm assuming you did; I'm assuming you made that decision based on literature that you read about use of ephedrine in weight loss programs.

DR. BRUNER: Exactly. Dr. Love had provided a great synopsis of that literature and I just, again, was familiar with it and there were some more recent articles in

a conference.

MR. FORD: Thanks.

DR. CHASSY: Do you want to turn to your own closing statement?

DR. BRUNER: Just really to summarize, I really said most of what I wanted to say. In the interest of time, too--I know that we're all anxious to get out--only that I'm very clear on ephedrine being used for therapeutic purposes. I'm still very unclear; is it a food substance, what benefit it has. We certainly do know--and I'm especially concerned in the weight loss industry, especially, because, as I mentioned, a lot of people--and I was involved with a lot of teenagers and phenylpropanolamine--do feel if one is more, two is better, three's great; let's do something to accentuate the loss. And I'm just concerned in terms of abuse potential, especially in that group.

DR. CHASSY: Dr. Hui?

DR. HUI: As a physician, I am distressed by the loss of even one life and I'm also very distressed by how a useful, traditional Chinese drug, when it was used inappropriately, is leading to its potential implication in, you know, the loss of lives and adverse reactions.

I do believe that herbs have a role in American health care, and I think knowledgeable use of herbs by

practitioners or citizens who know how to do it can, you know, enhance their health. But inappropriate use, and even knowledgeable use, appropriate use, you know, in some situations can lead to problems, and we just need to have a better law, modification of the existing law, to try to have a comprehensive strategy to deal with the role of herbs in this country because the patients are going to do it. They are doing it when they are not getting the results that they want and we just have to try to look at it in a very comprehensive manner, from the consumer, to academia, to industry, and also the scientific establishment.

And I really would like, you know, to emphasize the need for education. We at UCLA have been teaching the physicians and nurses about herbal medicine and its relationship to pharmacological use. We are teaching our patients and the public about appropriate use of herbal products, and I think it's in the system and you have to deal with it and I just think that if you ban it, it will go underground and we will have a more tough problem to deal with. Thank you.

DR. CHASSY: Dr. Fong?

DR. FONG: If it is possible to be on both sides of the fence, I find myself in that situation today, which is not normal. I am very much concerned about the lack of

quality assurance and exaggerated claims of a number of the ma huang products presently available in the United States. On the other hand, as a pharmacognosist and a person who has been consulting with the World Health Organization program on traditional medicine, I am very afraid that if we take precipitous action and make ma huang or ephedra disappear from the American scene, this would deprive, as my colleagues to my right have said, herbal remedies that can be self-medicated.

In an idealized world, or idealized United States, I would like also to see the law changed so that we have a traditional herbal medicine category, like the Canadians do. Perhaps with something like that available, we wouldn't need to hide the botanicals under the guise of food supplement. From my naivete, my understanding is currently a lot of your botanicals are available as food supplement because there's no other place to legally sell it. So perhaps maybe we are here today to address the scientific issues, but perhaps more importantly perhaps FDA can help and push through the legislative process, or whatever the mechanism is. Thank you.

DR. CHASSY: Thank you. Dr. Dentali?

DR. DENTALI: Thank you. I have to agree with Dr. Fong, and I find myself again wanting to echo and reinforce

the comments brought up by Croom and Jasinski. When I came here, I understood that my mission is the common-sense one, is to reduce the risk with these products. So when I got the updated version of the adverse events, I wanted to do a rigorous analysis of those, particularly with respect to the October recommendations.

For me, that would be to look at the adverse reactions that are consistent with ephedrine use and to eliminate the ones that are not, to look at ones that are consistent with the levels of ephedrine that were recommended in October or that were proposed by a few members and eliminate those that were not, to look at the ones that were combined with other known stimulants and eliminate those reports, to look at the ones that were resulting from clear abuse and to eliminate those, to look at the ones that were made with only the herb and the herb extract and to include those and exclude all the others, and to exclude the ones that were resulting from chronic use.

And I feel that that wasn't done and I feel that that was very important for me to be able to have a handle on beginning to look at the risk as it was presented to me regarding the adverse effects for us to determine for traditional use and traditional forms what is the danger of using this botanical. So in that sense, I agree with Don

Jasinski and I hope I'm not overstating what maybe he was feeling.

Also, I'd also like to point out that quite clearly there are inappropriate uses, forms, combinations and marketing that's going on here regarding, quote, "these products." I just want to have us keep an eye toward inappropriate and possibly appropriate uses. I feel possibly that the food advisory--what I see is that we have a chemical, ephedra, that has given a black eye to an herb, that has given a black eye to an industry, that has given a black eye to DSHEA, when, in fact, herbs are a minor part of DSHEA. Herbs and clear drug herbs are a minor part of herbs. It's rare that we're going to be able to find an herb where we can talk about the active compound with a reasonable assurance that we're really going to encompass most of the pharmacological activity present.

So this is good. I mean, this is the test case that we can come here and talk about, and I'm not sure that it will continue in this fashion for all the other botanicals that may be of interest to the health care of the American public.

The other area that I feel that didn't receive adequate scientific attention was the differences between the herb, the herb extract, and ephedrine. I alluded

earlier that there were some studies that showed some differences. I have those here. For anyone that would care to have the references, I'll be glad to pass those on--the usual of what--the myth that I had always been told of slower uptake, lower levels of in this case ephedrine, longer duration of action, things of that nature.

One thing that occurred to me--on a practical matter, if we're going to limit dosages of ephedrine to maybe lower than what's found in the herb traditionally, then it's quite possible that the marketplace might extract ephedrine alkaloids and give the leftover material as an extract, particularly when this has already been emblazoned in the public mind as something good for weight loss.

In this case, we would have an extract concentrated in other ingredients with lower amounts of ephedrine and I'm concerned about the safety of such a product. There's a Japanese report here of acute ephedra herb and ephedrine poisoning in mice where they looked at the two. The value for the LD-50 for the extract was 5.3 grams per kilogram, and for ephedrine was 689 milligrams per kilogram. Now, if we look at those values, the amount of ephedrine alkaloids for ephedrine, pseudoephedrine and norephedrine add up to 236 milligrams per kilogram.

So in one case, the extract containing 236

milligrams per kilogram is causing an LD-50 equivalent to 689 milligrams per kilogram of the pure alkaloid. So if we're having preparations out there that are stripped of alkaloids becoming present on the marketplace, they indeed may be more dangerous than ephedrine itself. So this is a practical botanical matter that I don't see has received any consideration here.

In addition, we talk about ephedra as if they're all containing--all the ephedra-containing species when, in fact, the domestic varieties do not contain ephedrine. I can quite easily see a marketer going out there, harvesting from the desert Southwest, making concentrated preparations and selling that to the American public for weight loss. Now, what are the toxicities associated with that? We're not going to have ephedrine to talk about there. Yet, I would bet that we could see some adverse reactions from that. So these are issues that, at first glance, maybe don't apply, but in reality and practicality, when you're dealing with botanical medicine and industry today, do come into play.

I'm hesitating a bit. I don't want to criticize the committee here. I feel that we've all done a great job and everything has been really appropriate with the information that we've had. It does strike me, though, that

the Food Advisory Committee is being put into a situation of having to make determinations on herbs and botanicals, and I have not seen in most cases a knowledge, experience, or even a familiarity with a history of herbal medicine in this country, the uses, the forms, and industry as a whole.

And I would hope that industry and FDA, consumers, and herbalists and everyone with a point of view can work together so that we can have an industry, a renaissance of the American herbal industry, which I think is what we're seeing the beginnings of, that makes sense to all of us and that we can design and develop some enlightened approaches. Thank you.

DR. CHASSY: Thank you. We have two people that need to catch a plane, so Dr. Wang.

DR. WANG: Thank you. I served on the working group last October and I do want to reemphasize the critical points that were pointed out at the working group regarding warning, and these label warnings, they're not consistent from product to product, and so we need to identify that. I'd also like to see that for those products that are in weight loss, maybe they should also take into consideration of the OTC proposed label warning for the phenylpropanolamine warning, and actually for these ephedrine alkaloid products it probably would require a lot

more, since we're talking about short-term exposures, also.

Now, at the working group, the street drug alternatives, they were not mentioned. We weren't aware that there were--we were aware of some of these products, but didn't realize that that wasn't what we were supposed to discuss about abuse. And my personal opinion is that anything that makes these high claims, that should be legal, and also I would agree that the GMPs, the formulations, and also no final food form--when I talk about diet supplement with the level I was proposing, I was thinking of a pill rather than the food.

Finally, I did review what the association has proposed. They did propose a 1-800 number. I think there is a lot of research needed. There's a lot more education needed in this area. I do like to see also that DSHEA be revised somehow, taking into consideration for those Chinese traditional medicines or traditional herbal medicines into a separate category so that they can be used under proper supervision and under knowledgeable professionals.

And, again, part of the DSHEA I'd like to see is also maybe amended that the burden--the industry should try to bear some of the burden, just like other food products, rather than say you prove me wrong and then we'll see. That's why we spent two days. I think due diligence--we can

be here a week and not resolve issues because some of these are medicinal use and not food. Thank you.

DR. CHASSY: Thank you. Dr. Hsieh, I believe you have no further comments, or do you?

DR. HSIEH: I have no more comments, and only to say that I would support the recommendations made by the special working group with consideration of what has been elaborated in the last two days. Thank you very much for very helpful and enjoyable discussions.

DR. CHASSY: Dr. Ricaurte?

DR. RICAURTE: When I first became aware of this situation eight months ago as part of the special working group, I must confess that my initial response was to be rather cynical of the industry. Quite frankly, my impression was that the marketing and distribution of these products really was disingenuous and I had concerns that, in effect, these ephedra alkaloids represented the consummate designer drug.

I have tried to keep an open mind. I've tried since beginning with those impressions to try to listen to industry's side and learn more about what the appropriate uses of these products are, not to regard them as drugs, but indeed as dietary supplements, as we've been instructed, and, when used as such, what are the indications.

I'm afraid that despite keeping an open ear, I'm surprised, actually, that today--instead of learning more about what the potential uses and why consumers would want to use these products, I'm surprised at the fact that a number of potential uses and why these compounds, products, have been distributed have been taken off the table, and I'm left with the question, well, why are we going to use the--why are these compounds then going to be on the market, given that they contain a pharmacologically active ingredient. I don't have an answer to that and it's a bit disappointing after all this time to not have an answer to that question.

So the pendulum has swung from one extreme of being very cynical to trying to regard this as a product, a dietary ingredient that should be used by consumers and not be over-regulated, not be in a position where the FDA or the medical profession or the scientific advisory group is put into a position of over-regulating something that adult Americans perhaps may wish to use under safe conditions. Those have not been defined.

Finally, I just want to comment on this issue of dose. I think as long as the concern for some of the use is misuse and abuse, I find it somewhat, again, disingenuous to make recommendations, well, we're going to limit the dose

from 20 down to 10 or down to 5. As a consumer, I don't have to be particularly adept in mathematics to realize that if now the tablet or capsule or a spoonful contains only 5 milligrams, I take 2 or I take 3 or I take 4. So the dose considerations and frequency of use suggestions, while I recognize that they're well-intended and I appreciate what the efforts are in terms of looking at the reality of the use of the product by a population of individuals who may be predisposed to misusing or abusing the product, I don't think those are particularly effective safeguards. Thank you.

DR. CHASSY: Mr. Israelson?

MR. ISRAELSON: I've spent my entire professional career struggling with these issues. Maybe I should get a new job. I don't know, but the regulation of botanicals has always presented a difficult task for the agency and I have to say historically it hasn't been handled with any degree of long-term thoughtfulness. And so many of the issues that you have raised and that you're concerned about are a reflection of that 15, 20 years of historical difficulty.

As an example, over four years ago a large group of European phytomedicine companies who produced drugs to drug standards in Europe approached FDA through a citizens petition seeking old drug status in the OTC review for

certain key phytomedicine products or plant medicines in Europe. Four years later, we still have no response from FDA. So your suggestion that we attempt to take this through the OTC avenue has been actually considered. A great deal of energy was spent to develop those proposals and we wait.

DSHEA was passed because millions of Americans were concerned that their access to products which they regard as useful was going to be denied or that information about those products would be unavailable. It became a very large and controversial issue, but at the end of the day the Congress recognized that many consumers were very concerned that, however they wanted to use dietary supplements for the varied reasons that many of you may not be familiar with--but indeed millions of Americans use a wide range of botanicals and other products for reasons important to them, and to second-guess that judgment becomes very problematic on the part of this or any other committee.

I have to say that the industry has and will continue to work with the agency to establish reasonable policies on ephedra and other botanicals. We have prepared a very recent draft which we have given to the agency which voluntarily dropped the dosage levels prior to this meeting in view of the more recent data that we were receiving, and

we were hoping to respond to their concerns and we did so. We'll continue to work with the agency and I share the view that has been expressed that if you ban this product, you'll drive it underground and create a bigger problem.

If you feel people are being harmed today, I believe it would be worse to do it by simply not recognizing this in some fashion. In my judgment and in my experience, it's better to create incentives for the industry to meet good-quality practices, and by the way there were some comments made today by one of the public speakers that I personally wish to disassociate myself with in suggesting that the quality of source materials and other things are essentially unknown, unregulated and unobserved by the companies who produce these products. And the companies that I know and the associations that I work with, that is simply not the case, and I was personally distressed by that and I wanted on the record simply to reflect the fact that that did not reflect the views and the practice of the broader industry.

I, like you, recognize this is a very tricky issue for lots of different reasons, and I'm concerned about the policy aspects of it and you're concerned about the medical and scientific aspects, but ultimately those two issues have to come together to find some rational way to resolve this

question with ephedra specifically and more broadly botanicals generally. I think ephedra represents the most complex and most difficult of all of the botanical issues and it's perhaps too bad, perhaps it's good, that we're dealing with it now.

There are many other botanicals that have well-known and recognized uses and benefits, but unfortunately, because of various policy reasons, they cannot be recognized as anything other than a dietary supplement for the present time. If you on the committee think that there are better ways to do it, I will gladly join you in efforts to identify means through OTC, through traditional medicine avenues and others that would appropriately place botanicals where some of you feel they ought to go.

So with those comments, I appreciate the hard work of the committee on a very tough issue.

DR. CHASSY: Thank you. Mr. Ford?

MR. FORD: I have heard a lot of characterizations and mischaracterizations today and yesterday going around this table, some of the witnesses, some people in the industry. I think that there should be a recognition of the fact that, first off, DSHEA--you know, you know the old story about legislation. It's like sausage; it tastes good on the plate, but you wouldn't want to see how it's made.

It's not a perfect Act, but the regulation of dietary supplements prior to its passage was far from perfect as well. One of the public speakers this morning made some very moving testimony, I thought, about the injury that his wife sustained.

There was, before DSHEA, an element of caprice in the regulation of the supplements that I think caused a reaction in the industry that now that there is regulation, I think we have the tools within the industry to bring about some changes. That may seem kind of odd to you, but there are many very fine, quality-conscious manufacturers and retailers in our industry who are interested in standards. They're interested in making our trade association based on standards so that belonging to it will really mean something, and they've put in a lot of time on the GMPs that we presented to the FDA that they will be using as the basis to develop the GMPs, to get comments on them from the public, that we hope will have the force of law and will help us raise the quality in the industry.

But there is a fringe element out there. You can't tell one from the other without a program, I suppose. The variety of injuries that we see in the reports come predominantly from products that are not part of what I would call this industry, which is not to say that there

aren't some products in the injury reports that are legitimate industry products.

I come from the addiction field myself from a different standpoint than Dr. Jasinski. I never treated anybody, lucky for them, but I was an advocate in that area and it is not to be laughed at, what can happen with banning something. For one thing, you can be called a neo-prohibitionist or a pharmacologist Calvinist, which Dr. Jasinski will certainly tell you.

But in Sweden, for example, they have not banned alcohol, but they have made it extremely expensive and if you get caught drunk driving once, you lose your license for a year; twice, that's it, it's gone. And the drunk driving has gone way down in Sweden; the alcoholism has not. So you have to realize that when you put these kinds of restrictions on a product, they're likely to come up someplace else, like squeezing the balloon.

I am a little disappointed at the way the process has gone, and I want to underscore that it has been very valuable. I was honored to be made a part of the--although non-voting, of the working group and to sit on the Food Advisory Committee, and I think you all have put in an incredible amount of time. And the expertise that many of you have on these kinds of issues, I think, is important,

but I'm disappointed that we've had a pretty open access to the FDA and that we have been able to work toward what I thought was going to be some solutions and I feel that since the October meeting of the working group, the issue has become less this herb, which should be of interest to this group, and more the law, the dietary supplement law, which I don't believe was a part of the charge of this group.

And it wasn't the lobbyists and the lawyers that got the Act into place; it was millions and millions of people who use these products with apparent safety. And I think what we're going to see--I'm going to tie it up right now for you--is the responsible part of this industry will absolutely and entirely comply with the law and whatever regulation is finally approved, whatever legislation is finally passed, we will comply. But I will tell you that there is another part of the world that has ephedra products that will keep this agency in court for so long that you will not see any advance on the formulation that is said to make these injuries occur without fail, and I think it would be best to avoid that. I can assure you the responsible part of this industry will not participate in it, but I can also assure you that it will happen.

DR. CHASSY: Thank you. Dr. Woosley?

DR. WOOSLEY: A sobering message. I want to thank

the organizers for inviting me to participate in this. This has been challenging and I compliment all of you for your stamina and dedication.

I would start by--I have really just one point, but I want to start by saying I agree with Dr. Ricaurte. I find it frustrating and I do find some of the problem in the industry to be a disingenuous taking advantage of herbal medicine, taking advantage of traditional Chinese medicine and trying to mask themselves as a food, a food supplement, when actually they're trying to sell energy, strength, ecstasy, which is not, I hope, part of the value that Dr. Croom was referring to.

I find difficulty with that because I don't understand what the medical value, the social value, the physiologic value of ephedra in a dietary supplement to be. That disturbs me a great deal because I don't--as I think you pointed out, Dr. Ricaurte, there is no risk/benefit ratio you can establish when you don't have a known benefit, and we talk about a benefit, but is it just feeling stronger? We know that when you take these stimulants, you do feel stronger, but you aren't stronger. You do not have greater endurance. You can't run faster, swim faster when you take these drugs. You just feel like you did, so why should we allow our population to mislead themselves when

they use these drugs and they assume?

When the public sees a product sold in a store in the marketplace, especially one that's labeled as a food or a food supplement, they really assume that it's safe and that it has been judged safe by the FDA. They assume that a committee like this has deliberated on it and really leaves feeling comfortable. So I think when we come up with a number, if the FDA decides to do that--and I'm really disappointed that Dr. Kessler is not here. I hope you'll pass on the message that someone on this group felt that we have to take a stand. It may not be a comfortable stand; it may not be the best one for an overall message from herbal medicine, but to say that there is a safe level of medication that is available to the public when we really know it can kill people is not being fair to the American public because they expect more of us and they expect better of us.

And I wish Dr. Kessler could have been here to hear Dr. Benedict's comments. I think they were poignant and they were real, and I share them because I have children of my own that walk into health food stores everyday and hear the garbage that I know is being portrayed upon them.

I think if the FDA agrees to a negotiated safe harbor or some, quote, "safe dose," the public will assume

that these dietary supplements can be taken safely. Yet, we know from Dr. Love's presentation that serious, life-threatening reactions can occur with products containing levels of ephedrine as low as 1 to 5 milligrams. We don't know why these people are having serious reactions and some of them dying, but we know they occur. So how we can arrive at a number that we're going to put on the American public? This would not be a morally acceptable option for me and I hope it won't be one for the FDA.

DR. CHASSY: Thank you very much. Dr. Inchiosa, please.

DR. INCHIOSA: Yes. I'm also frustrated about a way of approaching this problem and I'm not at all too proud to compliment the fact that the Canadians have tried to look at it in a logical or systematic way in developing a separate category. I think the advantage of that separate category of traditional herbal remedies is important philosophically when a person, a consumer, goes to buy a product which is labeled as a remedy, they realize that they're taking it to cure some condition.

It starts with the premise that they have a problem that they perceive and they're going to give this entity a try. It's very much the same way when you shop in different places for over-the-counter drugs than you do for

nutritional supplements; they're in different stores. Even when a parent buys an antihistamine and looks at it at the supermarket shelf--and there's an amusing aspect here. We are so sensitive and sophisticated as consumers that my wife tells me when I buy Benadryl to make sure it has no artificial color in it, so we're very sophisticated and I think that is part of what you were saying, Dr. Woosley, that we have a great expectation that someone is looking out for our safety.

We really rely on the agencies. We rely on the environmental agency, the testing of safety of cars. We expect quality. We don't expect that we're buying something which is masquerading as something else, and so I think that has to be solved and I think the only way to solve it and still be able to maintain the validity--after all, as a pharmacologist I come from a tradition which included digitalis leaf. I mean, it isn't as though we don't know that we make our ways through recognizing new pharmaceuticals from various approaches, many of them being from natural products.

And the point has been made that maybe there are other aspects of ma huang, and I think in an appropriately regulated circumstance that can continue. And, in fact, reducing the levels of active principals to where there is

no chance of a success doesn't mediate toward recognizing any use of botanicals as well. So I think in the context of a risk-to-benefit circumstance, with some reasonable assurances of safety, as we heard were outlined in the Canadian situation--and apparently the FDA appears to have some mechanism in place which could handle a non-traditional or unorthodox preparation or an alternative preparation.

I think there is that route, so I think we are left with the situation that there is a route for marketing botanicals in the framework of some evidence and scientific information, and so then we're left with the concern which I think has been overexaggerated of driving it underground. First of all, I'd be very disappointed that we would react from fear alone. After all, we do regulate many drugs of abuse. We regulate everything. We regulate all the opiates, cocaine. There are schedules for all of these drugs. Everything is regulated that is considered to be unsafe or have risk, so we already do that.

The interesting thing which I believe I'm correct about--and I stand corrected, if necessary--that in the experiences in Ohio, the Canadian study, even the information collected was that young people who are abusing the drug largely get it from ephedrine hydrochloride from over-the-counter preparations. I heard that statement made

that a large number of the use by young and abuse by young was from over-the-counter preparations, not the difficult process of extracting something from a nutritive supplement.

So, therefore, the underground already exists and I don't know how much we're going to drive it more by an orderly process which would direct botanicals to their own control. And so I feel that it's a time for taking that step. I know it's a drastic step, but I think if it is combined with a process that allows for appropriate development and availability as a therapeutic remedy, it will, in fact, perhaps--well, first of all, it will be much more honest in the intent and it may actually help to develop a policy for botanical control.

DR. CHASSY: Thank you. Dr. Marangell?

DR. MARANGELL: Yes. I very much agree with Dr. Benedict and the two previous speakers on a number of points, and I think we are addressing several different issues which are intertwined, one regarding the potential abuse. We can also deal with the pharmaceutical ephedra as well, although that's not our charge today.

I don't find the underground argument very compelling, for the reasons that you just articulated, but also with opiates and other substances. When you go into a store and you buy something, the perception is very much

that this is safe, that this is a safe product to take. If you go to your drug dealer in the back parking lot, you should very well know that it is not regulated and it is not necessarily safe and it's not necessarily a Chinese herb. They are different things and I don't find the argument of going underground one that is legitimate in this discussion.

I do support allowing the public access to herbs and traditional Chinese remedies, and again I was impressed with the Canadian system where an herbal product can be either an herb or a drug. And the definition of an herb is something that can be taken by most people safely and if something has a pharmacological effect, whether it be synthetic or botanical, it is considered as a drug, and what we've been talking about are pharmacological effects of these products.

I don't think that we necessarily need to go through the same rigors of drugs and, as the Canadians have done, I would agree with setting up a separate division with separate policies for botanicals. And you can use, as you do with grasses and food products, something with--a different herb with a long tradition of safety does not necessarily need prospective data. Something where there is concern, you would want to have more rigid controls over, and certainly controls over manufacturing, assay amounts, if

that's possible, if that's what you're trying to look at, the quality control measures that we've all talked about that are not in place right now. And I believe that because of that, the current products are an eminent danger to public health as they stand.

I think I had one more comment. We've been talking about the numerator and denominator, and in my assessment of this I agree the data is very poor, but I think the numerator is surprisingly high, given that all the FDA is allowed to do is a passive surveillance system. My understanding of the law is that the FDA's hands are tied and that creating something like a different network or a different way of regulating this would allow us to get better data and pharmacokinetic data, if need be, for those herbs that have pharmaceutical effects and that are being marketed that way. In terms of--yes, that's--I think we're getting an underreporting of the numerator. I just wanted to point that out. I'll stop there.

DR. CHASSY: Thank you. Dr. Potter takes a pass. Dr. Guzewich?

MR. GUZEWICH: Get comfortable.

[Laughter.]

MR. GUZEWICH: First of all, I want compliment Dr. Love on what she's trying to do in running a surveillance

program. I've been doing that for 16 years for food-borne disease. It's not an easy task and she has a very difficult and often thankless job, and you're reporting for poor quality data and when it's the only data you can get a hold of and you're trying to make decisions on that kind of data--and I know where you're coming from.

I also want to compliment the FDA on the expertise of the panel that they brought together. I think we have some tremendous expertise around the table. I've learned a lot here not just from the FDA presentation and the other presenters, but people around the table, I thought, with tremendous expertise that helped and influenced me a great deal. So I compliment the FDA and the panelists for their expertise.

We were asked to comment on whether we agree with the levels or the recommendations of the former committee, and I agree with all of them except the levels. The other findings that there was an association, and so on--I agree with that, but the levels I don't agree with. DSHEA is a big problem, people. However it was intended, whatever its genesis is, DSHEA is a big problem because both the food industry and the drug industry are right now talking about products that they don't want to have to put through the food approval process or the drug approval process that they

can market under DSHEA and avoid the regulatory process. So it's creating a safe harbor, as was suggested for another analogy a minute ago. I agree with a lot of people around the table, particularly Dr. Ricaurte and Dr. Woosley's last comments.

Other comments: There were some comments made in some of the testimony that consumers can already buy other hazardous products in the marketplace, like peanuts and shellfish, things that cause allergies, food allergies. You should be aware those are things that physicians can diagnose, and when physicians diagnose them they can alert the patient to these associations and the patient can avoid those problems. And FDA has food labeling laws and USDA has food labeling laws that require the contents of those things to be on the product so the consumer can look at the product and say, hey, this has peanuts in it, I shouldn't eat it, or this is shellfish and I shouldn't eat it. So there is a regulatory mechanism in place, long established, for those kind of problems that helps people avoid the obvious potential health consequences.

It also was mentioned the idea that olestra was allowed in the marketplace. That's true, but the side effects from olestra that we heard on the panel last year don't quite measure up to the ones that we heard with regard

to potentials with ephedra.

Adverse event reports are a problem that the group has discussed a great deal. As I said a minute ago, I've been involved in surveillance for a long time. We know how to sort out the good from the bad there. I understood that we were seeing both the good and the bad, and I do believe that there was a consistent pattern associated with adverse effects from the ephedrine known effects that were reported by the experts here.

I'm particularly struck by the fact that there was a similar panel FDA convened a couple years ago that recommended that OTC ephedrine products be removed from the marketplace. I actually heard testimony from the Chair of that committee in another setting a couple of months ago. Part of the reason they did that was because of adverse effects. Now, I know FDA has not acted upon that at this time, but it is a recommendation from a similar advisory panel. That has a lot of influence on my feeling about the setting here. That was in a drug setting as opposed to a food setting.

I think that a lot of people have spent time talking about the customary toxicologic approach to determining a safe level, but I heard expert advice from this table that suggests that you can't use those linear

associations because there are people with inherent susceptibilities that don't allow you to use that linear association. So we kept going down and calculating these low levels and trying to go lower, lower, lower, but I think that missed the point that was raised at the table that that isn't a relevant kind of analysis to do for this particular product and the sympatho--

DR. POTTER: Sympathomimetic.

MR. GUZEWICH: --sympathomimetic--thank you, Maury--compounds. Dr. Potter and I go back far too far.

One of the things that impressed me that hasn't been brought up by the other panelists that was brought out is that some of the patients who were exposed to this product showed positive dechallenge and positive rechallenge, and not enough people brought that up. That also impressed me to show the strength of association. So although we don't have a lot of strong cases, the cases that were shown do have plenty of reason to believe something was going on there.

I'm very impressed by the fact that the effects can occur at any level and in persons who don't know they are at risk. That's a very important thing, folks. We're now talking about something out in the marketplace. It's one thing if you know you're at risk. It's one thing if you

know you have hypertension or some other condition your physician has diagnosed and you've been given advice about how to conduct yourself. But when you're walking around with unknown risk and there's a product in the marketplace that could light that off, that's something we have to think about. It really bothers me that we could put a product like that in the marketplace. Therefore, that's why I conclude that it's clear to me that there's no safe ephedrine level.

Consumers--this was brought up before--consumers and physicians assume a product on the market is safe or it wouldn't be there, and we heard testimony from more than one of the witnesses in the last two days where they told stories of consumers who told their physician that they were buying this stuff in a health food store and the physician said, well, then it must be okay. People assume that things there are safe. That's a very, very important concept in our culture, in our society.

There was a recent series of airline crashes that I'm sure we've all heard about and one of the things that people questioned was the regulatory system, and one of the things you saw in the media and the press is is the regulatory system protecting us and the FAA took a lot of scrutiny from Congress and a lot of heat about is the

regulatory process protecting us as consumers. We get on these planes. We can't know all the sophisticated things about airplanes.

Consumers walking into an herbal products store can't know all the things about herbal products. Now, they can make choices among safe products, but sophisticated choices about products that might be at risk to them, I think, is more than we can reasonably expect consumers to have to assess when they choose between different bottles on the shelf. Therefore, consumers should be able to purchase a product in the market and find it safe at normal use, and even at abused levels, given all the considerations we have talked about on abuse.

And because of those reasons, and having regulated foods now for most of my 26-year career, I can't see being part of a system that would recommend a product in the marketplace that could put consumers like that at risk. I don't think we're living up to the responsibilities at least that I have as a regulator that I could, in good conscience, recommend that kind of an activity. I understand there's ramifications. I have no particular interest in overregulating. I have no particular interest in damaging industries or putting people out of business.

I came from a dairy background and I've been

involved for a long time in fighting raw milk because I think it's not a good thing, even though it means that some farmers can't sell a product that they want to be able to sell. Similarly, here I think we have a responsibility to the consumers that only safe products are available for them to choose among and the free market reigns, the free market reigns. Thank you.

DR. CHASSY: Thank you. Ms. Richardson?

MS. RICHARDSON: First, I'd like to say that I think that we do need a category for botanicals. I think certainly a lot of the confusion with regard to the dietary supplements that contain ephedra would not occur again. I also think that it's important that the botanicals are looked at and classified.

I come from an ethnic background that has a tremendous respect for herbal medicine. I am also a geriatric nurse and I know that consumers believe that if it's in a health food store, it's healthy, and I see that with my elderly patients. I see that with the women that I work with everyday. As a geriatric nurse, though, I administer dietary supplements to maintain nutritional status, promote healing, and to prevent weight loss. I also know that my patients, the women that I work with, see TV ads all the time that are promoting dietary supplements.

The things that we have talked about today that contain ephedra are not Ensure or SustiCal or even Boost, and they're not multi-vitamins, and so to call them dietary supplements, I think, is misleading to the public.

I would encourage the industry to pursue the clinical trials on ephedra. I think it would certainly be tremendously helpful. Certainly, we know that FDA can't fund it. What we would hope is that the industry can fund the research the same as the pharmaceutical does and the food industry, and I would certainly be interested in them following Dr. Jones' assertion that the Department of Health and Human Services in a study on ephedrine found that it significantly increased the survival of female rats. It's probably the only study that HHS ever did that they used female rats.

[Laughter.]

DR. CHASSY: Thank you. Well, most of the things that I would have said have been said very ably by people around the table so I'm going to end up being a little repetitive, but I want to address some remarks to some of the players in this play that we've all been part of, probably to the audience for great patience. After those remarks, I know that Dr. Shank wants to address the committee and then we should be able to adjourn.

Let me first make some comments to the FDA, and particularly the FDA staff who has done a tremendous job both in assembling this panel and in getting together information, getting it out to us, trying to analyze the information literally on the run, under the gun; as others have said, very, very difficult information to collect. As usual, they've pulled a rabbit out of a hat, but I would encourage them to keep working it very, very hard.

Several have noted the quality of the data, and without blaming the FDA staff in any way because they are to be commended, they need to build a cause-and-effect relationship, however hard that may be. I think they especially need to do it because DSHEA sets us in a situation where they may find themselves in court being asked to bear the burden of proof that the ephedra alkaloids have done damage in a specific case, and they may find themselves doing that again and again and again. I'll return to that point.

On balance, having listened to medical expertise here, I'm not sure that the FDA would really not be remiss if it did not make ephedra alkaloids and ephedrine-containing drugs prescription items across the board. It would be very hard after hearing what we've heard and after hearing the conclusions that Jack just referred to, the

study a couple of years ago, to accept continued over-the-counter or dietary supplement sales of ephedra, absent more information.

I think there's one specific thing the FDA really ought to be doing, and I think the industry probably really wants to do the same thing. It's one of the reasons responsible members of the industry have an association and are trying to enforce standards, and that is that anything out there that is adulterated with ephedrine as the hydrochloride or the sulfate ought to be tested for--a virtually impossible task at this point, I agree--by the FDA and ought to be culled from the market. It is adulterated and it is mislabeled and misbranded, and it only hurts the industry and that's why they would like to see that done, but it is not an easy task to do and I recognize that. I would give that a very high priority, although it may become moot if we make this a prescription item that we're talking about. If we don't do that, then I think we have to cull out the bad seeds who are spiking the product, and it's out there.

I'd urge, finally, the Commissioner to stand his ground and seek a pragmatic, but not a political solution to make this a science-based regulatory decision, and he has done that in the past. He does not shy away from doing

that. I have every confidence he will, but this is one where I think he really needs to do what he asked us to do, and that is look at the science of it and look at the medicine of it and then take the lumps of whatever decision that that dictates.

To the committee, I would say I am impressed by how many of you were able to ferret out from the data that we were given conclusions with which I largely agree even though there were, in general, two schools of thought here; one, the school of thought that said that a very low dose might be appropriate, and the other that they could find no dose which would be appropriate.

I think one of the reasons for that difference, though, from my point of view anyway, is that the committee did not entirely accept its charge and address itself to the scientific issue at hand. It was not our concern whether we would drive a drug underground, whether people would find it in other ways. It was not our concern to leave a drug or a dietary supplement in the market because many, many people used it and would want it. We were asked to make a very difficult scientific determination about safety and about risk, and I think in the end we all did that, but I think those other factors were not germane until this round of discussion. And then they are obviously very important in

the larger picture, and I agree with much of what you've said.

To the industry, I think you're to be commended, those of you that have represented organizations that have banded together to take what is really a fledgling industry--it's just a few years old--and to make it into a group of reputable manufacturers and retailers who deliver a value-added product to the American people. And given the frustration that you may have had with the regulatory system, as Mr. Israelson mentioned, in even getting the ruling, I think you're to be further commended for staying with it and showing the spirit of being willing to work with the agency and this committee to try to arrive at a solution that's fair to both your industry and the consumer and to the scientific and medical considerations.

I did, however, feel that you have a blind spot, and it's a blind spot at what low levels of this drug do and it's a blind spot to what first doses or the first week of dosing do, and I don't think you do yourself any good to have that kind of blind spot. What the evidence indicates is that there is clearly a smoking gun, if in only a few cases, and I think that's the problem that the committee had problems with. Those few cases were sufficient to say these were effects which we might understand in an over-the-

counter preparation, we could probably understand in a traditional medicine preparation, but we cannot understand in a dietary supplement--neither understand nor accept.

I don't know how far the two gentlemen that are at this table will want to disassociate themselves from two of the speakers this morning who told us one other thing, and that was--and I made reference to this before--that, well, the burden of proof is, in fact, on the FDA and that besides driving ephedra underground, what we may well do is drive the FDA into interminable court battles and you prove that it's unsafe.

That is, in fact, what is wrong with DSHEA, as I see it, because we talked about a clinical trial and the industry is all for that, and I think there's a problem with the clinical trial and the problem is the comparative safety of ephedra and ephedrine alkaloids means--and it's very clear that many people can take these products repeatedly without doing any damage. I mean, there are millions of people taking them. That means that in order to do a meaningful clinical study of the effect of taking these products on people, it would have to be enormous to get the statistical power to see the adverse effects in a controlled clinical study. You cannot do that study; it is incredibly expensive.

But Congress has provided a remedy for you; it's called DSHEA. You're doing the clinical study on the American public right now. This Act is, from our normal perspective or regulating drugs, backwards. We put the product on the market, we collect adverse reactions, and when we've got enough of them, then we take a look at it, and that's bad regulation and it's bad law. And I'm going to make it a personal objective to try to do something about that and I think it would serve the industry very well and all of the rest of us very well to be doing exactly like that. There are aspects of DSHEA that are perfectly fine, but I don't think it was intended for this particular kind of product, and I don't think the manufacturers do either, and we would be much better off with, as others have said, an herbal medicine category.

If we can't do that, I want to close with one last amendment to DSHEA that we might put out there, and that is to simply require that we have a diamond-shaped yellow sign on health food stores that says, "Caution, federal authority ends here."

DR. YETLEY: I was just going to make a couple comments and then I'll--

DR. SHANK: Make them short.

DR. YETLEY: I'll make them very short. I just

wanted to thank everyone for participation in this committee meeting, and particularly to those of you that are so tenacious and hardy. We really appreciate your effort. I think we got an incredible amount of information that we can take back and use.

I also want to express the sentiments of both Mr. Schultz and Dr. Kessler. They both indicated to me as they had to leave that they found this meeting extremely helpful. They found the comments to be thoughtful, to be in-depth, and the broad range of comments to be very helpful. So, again, thank you.

DR. SHANK: That's what I wanted to come to the table for. Again, I've got the most honored role of this committee, and that is to thank you for the job that you've done. I recognize that we're about 90 minutes beyond our scheduled departure time and I'm not going to sit here and make sure that Jack has someone to talk to until his plane leaves, or John leaves later tonight, but I do want to draw attention to two points during the summaries.

I think that the summations that we've heard demonstrate two points, without question, and that is the complexities of the issues that we're dealing with. There are not simple solutions and that's the reason we call on people like you to assist us. The second observation is the

energies or the conviction that you brought to the deliberations the last two days. Those two different types of characteristics of this problem, the dedication that you brought, certainly were demonstrated during the work during the last two days and I would suggest were highlighted during the summation.

Again, thanks for all the hard work not only to our standing committee, but to the experts, to the industry representatives, and to all of those who participated. We thank you very much.

DR. CHASSY: I'll turn the Chair over to Dr. Larsen.

DR. LARSEN: The meeting is adjourned.

[Whereupon, at 4:57 p.m., the meeting of the Food Advisory Committee was concluded.]