PUBLIC MEETING

ON

THE SAFETY OF DIETARY SUPPLEMENTS

CONTAINING EPHERDINE ALKALOIDS

VOLUME I of II

Date: August 8, 2000
Pages: 1 through 298

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CONTAINING EPHEDRINE ALKALOIDS

VOLUME I of II

Tuesday, August 8, 2000

U.S. Public Health Service
Cohen Building Auditorium
Washington, D.C.

The meeting in the above-entitled matter was convened, pursuant to notice, at 9:00 a.m.

A G E N D A

Public Meeting: Safety of Dietary Supplements Containing Ephedrine Alkaloids

Tuesday, August 8, 2000

8:00 am	Registration
9:00 am	OPENING **Wanda K. Jones**, DrPH, Director Office of Women's Health
9:10 am	Ephedra-containing Compounds: Historical and Pharmacologic Context **Harry H.S. Fong**, Phased, University of Illinois, Chicago
9:50 am	BREAK
10:05 am	Adverse Event Reports: Database and Clinical Studies **Lori A. Love**, MD, PhD, FDA **Julie G. Bietz**, MD, FDA **George Ricaurte**, MD, PhD, Johns Hopkins University School of Medicine **Raymond L. Woosley**, MD, PhD, Georgetown University School of Medicine **Cynthia Culmo**, Texas Department of Health
11:50 am	Q&A
12:10 pm	LUNCH (on your own)
1:10 pm	Adverse Event Reports: Ephedra Education Panel of Experts Review **Steven E. Kimmell**, MD, MSCE, University of Pennsylvania **Theodore M. Farber**, PhD, DABT, Toxichemica International **Norbert P. Page**, DVM, MS, Toxichemica International **Grover M. Huchins**, MD, Johns Hopkins University School of Medicine **Steven B. Karch**, MD, City of San Francisco **John W. Olney**, MD, Washington University Medical School **Edgar H. Adams**, MS, SCD, Harris Interactive
2:55 pm	Q&A
3:15 pm	BREAK

Public Meeting: Safety of Dietary Supplements Containing Ephedrine Alkaloids

3:30	Abstract Session I
3:30	Barbara J. Michael, HEAT
3:45	Q&A
3:50	James S. Turner, Swankin & Turner
4:05	Q&A
4:10	Linda Golodner [Brett Kay], National Consumers League
4:25	Q&A
4:30	Col. Esther F. Myers, PhD. RD, FADA U.S. Air Force
4:45	Q&A
4:50	Adraine Fugh-Berman, MD National Women's Health Network
5:05	Q&A
5:10	Michael McGuffin, President, American Herbal Products Association
5:25	Q&A
5:30	Robert M. Stark, MD, FACP, Yale University
5:45	Q&A
5:50	Public Comment Session A
5:50	1. Samieh Wood, Private Citizen
5:53	2. Hanna K. Zewchzer, Private Citizen
5:56	3. David Molony, American Association of Oriental Medicine
5:59	4. Pablo Francisco Semiao, Private Citizen
6:02 p.m.	Adjourn

LISTENING PANEL

Chair: **Wanda Jones**, Dr. P. H.
Deputy Assistant Secretary for Health (Women's Health)
Director of the Office of Women's Health
U.S. Department of Health and Human Services

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P R O C E E D I N G S

[Time noted: 9:00 a.m.]

DR. JONES: Good morning, everyone. My name is Wanda Jones. I am the Director of the Office on Women's Health. We are here to address the available scientific information on the safety of dietary supplements containing ephedrine alkaloids.

During the course of this two-day public scientific meeting, we hope to have four specific questions addressed by the many individuals and organizations who have come to provide information. These questions are: First, what positive and adverse physiologic actions would be expected of ephedra based on its known constituents? Does the available information show an association between the use of dietary supplements containing ephedrine alkaloids and adverse events, that is cardiovascular, center nervous system, psychotropic, or other events when used as directed.

Second, are there any circumstances for which there are well-established indications for the use of dietary supplements containing ephedrine alkaloids? What does and duration of use are needed for those indications and what is the quality of any data to support such use?

Third, how would one characterize the seriousness and/or severity of the risks of ephedrine alkaloids labeled for weight loss and exercise enhancement taking into account issues such as user demographics, age, sex, or race ethnicity, the amount consumed across the population, use with other natural or synthetic stimulants, such as caffeine, synephrine, yohimbine, or the added stress of exercise and individual sensitivity to these types products?

And, fourth, are the outcomes associated with these products affected by dosage, by user characteristics such as age or predisposing health conditions, or behaviors such as combining use with other stimulants or other compounds? Is it affected by the duration of exposure or by others means?

Well, you may be wondering why we in the Office of Women's Health, at the Public Health Service, Office of Public Health and Science is convening this forum. Well, many women take these products as dietary supplements which makes this issue central to the immediate and broader public health concerns of the Office on Women's Health.

In addition, since the purpose of the meeting is informational and not regulatory, it is more appropriate for this meeting to be held outside of a

regulatory context.

Of course any data obtained during our discussions over the next two days will help the Food and Drug Administration in it's ongoing assessment of ephedra. And so we'll deposit a record of this meeting in the FDA docket.

As we begin our discussion today, it may be helpful to provide a brief historical overview of the key events that have brought us here. In 1997, FDA published a proposed rule that addressed the safety of dietary supplements containing ephedrine alkaloids. This proposal mainly suggested limits on dosage and use. A copy of this Federal Register proposal is provided on the information table in the registration area.

In response to the Federal Register announcement, FDA received numerous comments from the public. In addition the General Accounting Office audited the agency's procedures in developing its proposed rulemaking. The audit raised a number of issues about how the FDA had arrived at its proposed dose limits and about the openness of the process.

In addition to the audit, new information collected by FDA, and the interest expressed by consumers, manufacturers, and health care providers led

FDA to withdraw a large part of the 1997 proposal this past spring.

The agency reopened the comment period to provide an opportunity for discussion and assessment of the information related to the safety of these products. And that has let to this public forum.

The purpose of our forum is not regulatory management, but rather an effort to obtain and assess all available information related to the safety of these products used for weight loss and energy. And to that end, the Office on Women's Health has brought together a panel of federal experts in pharmacokinetic, epidemiology, toxicology, nutrition, and behavior, preventive medicine, and clinical pharmacology to assist us.

The role of this panel is to listen, to guide the discussion within the context of the four specific questions we have asked and to seek clarity where needed.

Let me take a moment to briefly describe the format and logistics for the meeting.

This morning and right after lunch presentation will focus on issues concerning the safety assessment of dietary supplements containing ephedrine alkaloids. Then we will have our first abstract

session followed by a few minutes of public comment. Tomorrow morning opens with public comment then there are abstract sessions, before and after lunch, followed by more public comment.

The speakers during public comment are numbered in your agenda. Tomorrow particularly, where there are a lot of you, there are numbered seats toward the front of the middle section and it will help move things along if you find the number that corresponds with the number that is preceding your name in the agenda and have a seat in that chair so that we can help move you forward as the public comment period proceeds.

It is my goal to start and the meeting and all presentations including the public comment as scheduled. We will be timing presentations, we have lights and signs that will be visible to the audience and the speakers to queue them about their remaining time.

We will try to flash the green light or show the sign when there are approximately two minutes left and give you a warning so you can wrap up, and the end on time. And a flashing red will mean stop. We want to be sure that everyone who has registered for time to speak has that some available to present his or her

views.

All speaker shown in the agenda should state for the record -- all speakers, no matter where you're from -- state for the record their name, affiliation source of funding for their activities, as well as source of funding for their travel here. Please be ready to come to the podium as your time approaches.

Because we had limited time for additional open comments, I would like to remind you that FDA welcomes your written comments and has reopened the public docket as of August 10th, 2000 through September 30th. This docket will display all of the information that the Agency has received including the information presented at this meeting.

We have also requested this meeting be transcribed. The meeting transcripts will be available to the docket as quickly as possible. We expect within 15 working days. Information about how to access the public docket and submit your comments is included with registration materials and certainly is on the table ins at the registration area.

Before we begin, I would like to extend a very special thank you in advance to everyone who has come to share their views with us. I am glad to see so many of you here this morning. I think I've talked to

virtually every one of you on the telephone. It has really been one of the most exciting things I've done in recent years.

We have attempted to assemble an agenda with a full spectrum of interested parties, and everyone, no doubt, has very strongly held views and very useful information for all us to consider.

We have relied in part on umbrella organizations including consumer organizations, professional societies, and trade groups to represent their members and to identify for us, panelists and speakers for this meeting. And we are very grateful for your cooperation.

I would also like to extend my thanks to all of the other people within the Department of Health and Human Services an the Public Health Services agencies, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, and the staff of my office who have contributed a great deal of time and energy to planning and making this forum possible.

And, now, a little housekeeping. No food and beverages are allowed in this auditorium, and I'm sorry, that's the bad news of the meeting. The restrooms are in the long corridors. If you exit the

auditorium, turn right, and go to that main cross area, turn right or left, and you'll see signs directing you to restrooms.

And then for lunch, we have a map available of places where you can grab a quick bite for lunch the are very close by. You'll need to wear you name badge at all times in the building, and to enter the auditorium.

For the deaf and hard of hearing we have interpreters with us today, Yvonne Robison, here in front of me, and Lisa Beth Schaefer, who will be providing sign language interpretation. So, if you do need interpretation please feel free to move forward so you can see them better because the lighting will not always be this strong.

If you have a medical emergency please let staff know. They are around and we can get you attendance. There is a very close by a clinic that we can be sure that your needs are taken care of.

And finally, I would ask that you turn off cell phones and beepers, or at least set them on silent alert for the duration of the meeting.

So let me underscore, we are here to listen, to guide the discussion within context of the four questions described earlier, and to clarify.

So, now, let me introduce the members of the expert panel who are with me here on stage. Starting at the far end, Dr. Paul Coates from the Office of Dietary Supplements at the National Institutes of Health; Dr. Harris Lieberman from the U.S. Army Institute of Environmental Medicine at Natik, Massachusetts. Next to him, Dr. Aaron Burstein from the Clinical Center at the National Institutes of Health; Dr. Mary Ann Richardson from the National Center on Complementary and Alternative Medicines at the National Institutes of Health; Dr. Berne Schwetz from the Office of the Commissioner and the Office of Science Administration from the Food and Drug Administration. And I am hiding here, Dr. Marcel Salive from the National Heart, Lung and Blood Institute at the National Institutes of Health.

Now, we do expect one other Panel member to join us but we will proceed until she arrives.

Without further adieu, I know that you're waiting for our first speaker this morning. Is that microphone work now?

Good.

It's my pleasure to Invite Dr. Harry S. Fong now to open the meeting with a background presentation on Ephedra-Containing Compounds or their Historical

and Pharmacological Context. And we've asked him to do all of this in about 30 minutes so that we can ask him questions if need be following his presentation. So it is a Herculean task.

Dr. Fong, welcome and thank you.

DR. FONG: Thank you very much Secretary Jones. I know this is politically incorrect, I was going to say my inspiration for public speaking is Elizabeth Dole the way she walks around. But this may not be politically correct and I guess -- well, I'll try to stand up.

I really appreciate being asked to come and talk to you. As Dr. Jones said we look at the historical perspective in pharmacology and I would like to point out that I come from a very unique place, the University of Illinois in Chicago and NIH Center for Botanical Dietary Supplement Research. I think we are one of two and Dr. Coates up there has something to do with us getting some funds. So let me make my public thanks and advertisement.

When Dr. Jones asked me to speak, she was under the impression that I am some kind of an expert. I will not disagree with her that I am some kind of expert, but at this point I think I should tell Dr. Jones what kind of an expert that I am. And expert by

definition is a person from out of town who is willing and able to say, "Have Slides Will Travel."

[Laughter.]

DR. FONG: With that out of the way, let me get down to my presentation. Is this mike working? Good.

Let's define what is ephedra. Ephedra is the dry area part of ephedra seneca or other related ephedra species. Ephedra has many names, vernacular names, the most famous of which is ma huang, a Chinese name. As you know it literally means -- the "ma" means the astringent action on the tongue; "huang" is the yellow color of the drug. Here is a stem of the ephedra seneca for the few of you who might not know what it looks like. I'm sure everyone here knows what the plant looks like.

In terms of geographical distribution there were more than 30 species distributed throughout the world particularly in Asia and even some in North and Central America; there are about 10 species in the Americas.

Try to give you a slight brief history. As we all know ma huang has been used for more than 5000 years in China as traditionally China's medicine for the treatment of asthma, congestion, colds, and so on

and so forth.

And ephedrine itself was isolated binding guide in Japan in 1887 and five years later or six years later Merck isolated pseudoephedrine from the same species in Europe. So you've got a world apart with the two alkaloids the two major alkaloids being isolated from the same plant.

In my opinion the classical and pioneering work which leads to the use of ephedrine was conducted by Dr. Kay K. Chen at the Peking Union College back in the early 20s and the introduction of this particular drug into Western medicine was followed the work publication in 1924 and 1930 by Chen and Schmidt.

In an effort to look for a more active or less toxic compound amphetamine was synthesized using ephedrine as the model in 1927. Then we jumped ahead to the early 1990s, significant to me is the promotion of ephedra and ephedrine for use as a weight reduction dietary supplements or as alternative street drugs.

Twenty-five years ago we had the pleasure of Dr. Kay K. Chin visiting us and giving us a very, very detailed recapitulation of his work in this area so I thought I would share a pitcher with you. Chemically speaking ephedra contains more -- could be up to more than 2 percent of alkaloids and the major alkaloids are

three stereoisomeric pairs, Ephedrine, pseudoephedrine, Norephedrine, Methylephedrine and Methylpseudoephedrine with ephedrine being 40 to 90 percent of the total alkaloid.

Let's look at the structure so that we are all in sync of what we are talking about. Ephedrine differs from pseudoephedrine by the stereo chemical configuration of the hydroxy group at a carbon 3 and a sci chain, and no ephedrine and no pseudoephedrine again the same difference as methylephedrine and methylpseudoephedrine and one note that the difference between ephedrine and norephedrine is the lack of the methyl group in norephedrine methylephedrine has a two methyl group so one look at the basic skeleton there it is all the same.

So one would expect that the biological activity or pharmacological effect are basically similar. There may be differences in the degree and the specific effects.

The occurrence of the different alkaloids vary from species to species. And this is just some example. I don't expect you to read this slide from way back in the room. I just want to emphasize in ephedra seneca, ephedrine account for about 60 percent of the total alkaloids and 65 percent of

pseudoephedrine being the second largest. In this particular slide the only species that has more pseudoephedrine than ephedrine is ephedra intermedia.

Now, what are the primary uses for ephedra, and it is proven effective as a nasal decongestant and treatment of various types of associated ailments and is a very good broncho dilator in the treatment of asthma. And a secondarily one can use it for treatment of -- narcolepsy and partial hypertension. But the primary use, I would like to stress as a nasal decongestion bronchial dilation.

Looking at an overview of the pharmacology of this type of compound, ephedrine and pseudoephedrine are major constituents, as I said before, and they along with the related compounds of potent sympathomimetic that act directly by stimulating the Alpha Beta 1 and Beta 2 receptors of athonergic receptors and more commonly by indirect stimulating the release of norepinephrine from neuron stores. And so it primarily acts like release of norepinephrine and then have some direct effect.

If one looks at the structure of epinephrine and norepinephrine compared its structures to ephedrine and pseudoephedrine one sees the basic carbon skeleton and the amino group being the same. The difference

being the hydroxy group in a side chain and the extra methyl group. So it's not surprising that they do act directly on the same receptors and a like we said, ephedrine and pseudoephedrine act primarily to induce the release of norepinephrine.

Now, I would like to emphasize that pseudoephedrine and ephedrine have the same spectrum of activity except that pseudoephedrine is a weaker compound when it comes to its hypertensive effect and the CNS stimulant effect.

Either compound on repeated dosing can lessen the biological effect because of the depletion of norepinephrine from the stores. So continuing use does not necessarily mean you will have the same effect.

In terms of women's health, the reason I think I was invited to women's health, ephedrine does effect the uterine muscle and consequently is being used to relieve the pain of dysmenorrhea. Every professor is allowed one slide where people can read. Dysmenorrhea unlike the red color to emphasize the condition, by you can't really see the red. So I'm sorry about that.

Ephedrine also stimulate the alpha adrenergic receptor in the bladder, small muscles, and one does increase the resistance to the outflow of urine so this

would be good in the management of incontinence or aneurin. But, unfortunately, for the few of us male in the audience one experience BPH and for those of us in that category one should refrain from using this type of compounds; it is tough enough as it is.

In the terms of cardiovascular effects they have the same action as epinephrine but ephedrine the action persists ten times longer than that of epinephrine and it is orally effective. The activities mediated by the release of norephedrine and the activation of both the alpha and beta receptors.

The alkaloid will stimulate the cardiac rate output and increase the peripheral vascular resistance and that produce a blood pressure rise. Elevate both this systolic and diastolic pressures and the pulse pressure as well. Most importantly is stimulates the systemic razor restrictions and one gets hypertension from overdose or excessive use.

Broncho dilation effect. The compounds ephedrine especially as a very potent branchial dilator because of its activation of the Beta adrenergic receptor in the lungs. The effect is less pronounced than epinephrine but it's so much to sustain longer both ephedrine and pseudoephedrine are useful as nasal decongestants, and due to the alpha adrenergic receptor

mediated razor constriction effect.

However, continued use of this type of material, let's say after more than three days continued use one can have a rebound effect. And if one relies on nasal decongestants as a medical aid, I don't know of too many nasal decongestants that do not call rebound effect. So one must use it judiciously.

In terms of the central nervous system effect ephedrine is already active as I said earlier. The important thing of ephedrine and related compounds stimulate the release of dopamine from the nucleus eccubens area of the brain. As the dopamine is released it then binds with the D1 and D2 receptors which then gives us the feeling of a well being and give us a high.

The ephedrine compound also activates the adrenergic receptors located in the CNS which also contributes to our feeling of well being.

Now, another CNS effect is with anuretic or weight and appetite suppression. Hence one has also a product like that.

Now, as I said earlier, the promotion of ephedrine and ephedra for weight loss was in the early 1990s. In terms of efficacy I have a question mark because I haven't read too many clinical reports. Of

the ones I could get hold of the effective weight loss is somewhere between four to ten pounds used over two to six months and some of the clinical studies also include a restricted diet, and so, make one wonder, is it the ephedrine or is it from the diet. But it definitely had some effect; how long it last I don't know.

Theoretically the ephedra type alkaloids is effective in that it has two actions. It has central enuretic effects suppressed to appetite which is one of the side effects of this kind of medication, it also has the peripheral thermogenic effect to burn up the fats, -- the triglycerides and so on and so forth.

I would like to make note that caffeine is a more potent thermogenic agent and perhaps that's the reason why they are put together. I would like to digress a little bit and look at the relative strength of the DCNS stimulant effect of various amines. As we said methamphetamine and dextroamphetamine will synthesize for a better drug.

And methamphetamine is greater then the ephedrine and pseudoephedrine and norephedrine in terms of the CNS effect. And, coincidentally, all of these compounds have been used as in weight reduction formulas one way or another.

I would like to point out that methamphetamine and amphetamine was really prescribed in the 1950s and '60s as an anoretic agent and they act primarily as to appetite suppression but the tolerance to appetite suppression develop very quickly. In the '50s and '60s I was a student at that time, a lot of us was overweight, so a lot of us did take the amphetamine but a lot of us also did not lose weight, a lot of us ate just as well as before. Not naming names or anything like that.

And phenylpropanolamine is another compound obtained from ephedra and it's been used since the 1980s as weight reduction with or without caffeine. Again, the effectiveness come in a question, in my opinion, because after three months of use they may not work anymore.

In terms of ephedrine and caffeine formulation the theoretical mechanism of action have scientific base because the ephedrine has the central anoretic effect, whereas, caffeine has the greater peripheral thermogenic effect so the combination should work. However I would like to point out that this type of combination product also have potentially a lot of adverse events of CNS and other anomic peripheral system events and it may have been synergistic CNS

stimulation between the two.

There's a study on the content of alkaloids and various diet products and one of the things that intrigued me was that there is a great variation of the content of alkaloids from one product to another even within the same product -- I don't know whether this product, herbal ecstasy, is still available or not, but you get two lots. One has a total different profile than the other and the contents of the ephedrine alkaloids are also quite different. You draw your own inclusion what this means.

Adverse events the principal adverse event to us is the CNS stimulation particularly the therapeutic index is very low. At two times the does one can have adverse events. Most of the adverse conditions are mild, particularly dosages 30, 60 milligram or whatnot one can have nervousness like I am having now even though I didn't take ephedrine this morning; one can have headaches, insomnia, dizziness, palpitation, skin flushing, tingling, tremors and urinary retention, so on and so forth. Personally I can't take decongestion of this of product. If I take and pseudoephedrine or ephedrine, my heart will be pumping a mile a minute. So there are idiosyncratic reactions.

The most severe reaction is hypertension.

That is the most important event caused by high dose or prolonged use. Arrhythmia and tachycardia also results and in the case of tachycardia and potentially death these events in our opinion used to be associated with the concomitant administration of other drugs like caffeine and antihistamine, and particularly then you dump in phenylpropanolamine along with ephedrine or so on and so forth. One can have an adverse event.

Now, the potential drug interactions of this drug ephedra, ephedrine is a drug. It's a CNS stimulant. Of course it should be not coadministered cardiacthycal like digitalis heart patients should not be taking this kind of stuff, people on sympathomimetic agents or among amino oxidase inhibitors among others totally contraindicated for that sort of thing.

Now, in conclusion, I would like to make a couple observations. Ephedra and ephedrine alkaloids are useful and can be very useful short-term sympathomimetic agents particularly in bronchial asthma as decongestants. The effectiveness as a weight reduction agent, I keep saying that it's a question mark because I have to see more clinical papers to convince me in terms of the risk to benefit ratio. It does work; people have lost a few pounds, but is that loss worth it.

In terms of mild/severe reactions it can be manifested as I said from both individual sensitivity or prolonged use or overdose.

One thing I absolutely do not recommend is the use or production of this product as street drugs. Thank you very much for your attention.

[Applause.]

DR. JONES: Thank you Dr. Fong.

Let me turn first to panel members, if you have questions for Dr. Fong.

[No response.]

DR. JONES: Let me turn to the floor. If you have questions for Dr. Fong there are microphones. If you would proceed to a microphone and ask your question, brevity is the should of wit for all of us.

Please proceed. Yes sir. Identify yourself if you would please the record.

MR. REINHART: Jeffrey Reinhart, People for Pure Foods.

Dr. Fong, would you comment or clarify on the stereo specificity difference between phenylpropanolamine and the plan of ephedrine?

DR. FONG: This high-tech stuff is good if you know how to do these things. Some of it just doesn't work the way I want it to work.

Phenylpropanolamine is low ephedrine, okay. The phenylpropanolamine and ephedrine has the same stereo chemistry. Is that what you are asking?

MR. REINHART: I was asking about the racemic situation with phenylpropanolamine. My understanding is that phenylpropanolamine used in commerce is plus/minus racemic mixture whereas in the plant it is minus.

DR. FONG: Yeah, okay. And you think that is a tremendous difference in pharmacological effect?

MR. REINHART: I think it needs to be elucidated, given the thalidomide issue.

DR. FONG: I'm sorry, I really can't at this particular moment in time I don't have the answer to be able to differentiate the difference between minus norephenephrine or the racemic phenylpropanolamine. But, you know, my conviction is that the difference of activity in terms of the at least the CNS stimulation and the cardiac effect will be not that great in terms of one look at the adverse effect and whatnot.

Now, I am not saying that phenylpropanolamine is not safe. I'm just cautioning not to use those things over a prolonged period of time or overdose.

Jerry, can you comment on the racemic versus minus? I have a colleague who used to be a professor

then he decided to go make money.

DR. McLAUGHLIN: Yes, I'm Jerry McLaughlin from Nature Sunshine products, now it's an herb company. See if my pointer will work here, here we go. So look at here, there are two asymmetric carbon atoms in the structure of ephedrine. Okay? Now, we can make different structures if we just switch one of those bonds around. Okay. So the ephedrine series are what we call erythrol, that is, both of these substitutions are going off in different -- actually in the same direction if we put all the carbons in a line. T pseudoephedrine have them going three out, or they go in different directions. Okay.

Now, one can go one way, and one the other so that makes four possible isomers of ephedrine if look at that. Now, we further complicate the structure by taking the methyl off, you see it's gone over here. Nor means that the methyl is gone. Okay? So, we end up with the nor servers. Remember, Harry also talked about the methylephedrines which puts another methyl on the structure of ephedrine here. So we end up with a huge mixture of all these compounds; and the plant doesn't just make one compound. It makes all these guys; okay.

So I think actually the structure of

phenylpropanolamine which is essentially this structure, but without defining the stereo chemistries in here giving us not only a racemic mixture of one carbon, but, you know, potentially more isomers all right; so you have at least four potential compounds in phenylpropanolamine. So I'm not really sure what phenylpropanolamine is; but if it does have a mixture of materials -- being synthetic it probably does -- it's probably going to somewhat mimic the plant because the plant makes a mixture of materials.

DR. JONES: Other questions either from the floor or from the panel?

[No response.]

DR. JONES: Seeing none.

DR. BRAY: Yes, good morning, I'm George Bray from Baton Rouge, Louisiana, interested in the problem of weight. My reading of the ephedrine caffeine studies that Arne Astrup, has published from Denmark would suggest that there is a statistically and clinically significant effect of the combination in his randomized, placebo, double-blind trial. I wondered if you comment why you put so many question marks because I thought that trial was about as nicely designed and executed as you could ask for in a clinical trial.

DR. FONG: Okay. That study that you're

talking about, yes, I have the question mark as a personal thing. The study that you're talking about is a valid study. My only question was that I think that be total weight loss was about five or seven kilogram of body weight lost as compared to the placebo. Now in the 33.5 kilo as compared to be placebo group there is statistics significance. My question mark isn't whether it does reduce weight. My question mark is how long the patients weight is taken off and maintained; and is five or six pounds worth the risk of adverse events over prolonged periods of time. Okay?

So I know I'm getting into a hornet's nest in this discussion. But it's just that for those of you in the audience, I was a member of the FDA ad hoc meeting about five years ago on regulatory aspect and my position was even ephedra and ephedrine are good medication and should not be banned from regulatory status. But on the other hand as a pharmacist and as a professor in pharmacochemistry I questioned that using an agent that has a low therapeutic index of two to three, usually I like to see an agent with therapeutic index of at least 10 to 1, this is my question mark not the statistical significance of the study.

DR. JONES: Further questions?

[No response.]

DR. JONES: I would note then that we are concluded on time. Dr. Fong it does appear that you have done the impossible and laid out a nice background for us for the day. I would send this now we're scheduled for a 15-minute break. It will give you a chance to get acquainted with the lay of the facility, to pick up the lunch map and everything.

When we come back after the break we will hear from our first panel that will look at adverse evening reports the database and the clinical studies as they appear in the docket that FDA has made available.

Thank you very much for your attention. We will see you in 15 minutes. We will be starting on time at 10:05 a.m. Thank you.

[Brief recess at 9:45 a.m]

DR. JONES: Dr. Julie Bietz, Dr. George Ricaurte, Dr. Ray Woosley, and Cynthia Culmo, shown in your agenda with discussion of the database and clinical studies and adverse event reports. Thank you.

DR. LOVE: Dr. Jones, panel members, and guests, this morning I will present an overview on the ephedrine alkaloid containing dietary supplements including new information in FDA's recent assessment of

the public health risk associated with the use of ephedrine alkaloid-containing products.

The complete documents from this assessment are available publicly in FDA docket No. 0091200.

As you can see from the slide, FDA concerns about the safety of dietary supplements goes back a long time. We first became aware of this issue because we received a report of a death in a young man who had been using a number of products for enhancement purposes, for athletic enhancement purposes.

In trying to evaluate the significance of this report, we noted that among the products he took, there were ones whose ingredients we were unfamiliar with. Ingredients like ma huang, for which we now know is a Chinese name for ephedra and contains alkaloids which were refer to as ephedrine alkaloids that are very potent sympathomimetic in means, as Dr. Fong has just explain for all of us.

Besides becoming aware that these ingredients were in these products, we reviewed the scientific literature which also raised our level of concern; and the other thing that we did was to look in available databases to see if there were other adverse events with this same product or with other products that contained this ingredient and we found cases of these.

So in 1993, I'm not sure if I know how to use this.

1993 was when FDA first indicated its concerns about the safety of these products. In 1994 we held a formal health hazard evaluation board that examined the safety of a particular product for which we had received a large number of adverse events. This was ephedrine alkaloid caffeine containing combination which was felt to represent a significant health hazard.

As Dr. Jones mentioned this morning, we have had a number of public meetings where we have discussed the data that are available on these. In 1995 we had a public meeting where we convened a special ad hoc working group of scientific experts that served as a working group to our Food Advisory Committee which is the general scientific advisory committee that we have in FDA. And at this time we really evaluated all available information. There really was almost a virtual absence of information at that time and I think still today that would indicate the safe use of these types products.

And it was the members' feeling at this working group that they agreed the use of certain dietary supplements known to contain or suspected to contain ephedrine alkaloids may cause consumers to

experience serious adverse events.

In the following year, in 1996, because of new information which included an increasing number of adverse events and product analyses indicating that the levels of ephedrine alkaloids were below the 25 milligram limits that had been suggested by certain members of the working group. The full Food Advisory Committee was convened. And, again, they reviewed all but available data information and provided their opinion on, and a rationale for specific ways that FDA could attempt to address the public health concerns with these products.

Over half the Food Advisory Committee members stated that, based on the available data, no safe levels of ephedrine alkaloid could be identified for use in dietary supplements and consequently they recommended removal of these products from the market. Other members of the Food Advisory Committee suggested that the agency establish conditions of use that would reduce the risk of adverse events including establishing reasonable safes, per serving, and daily use levels for both ephedrine alkaloids and ephedrine as well as other requirements.

Out of these public meetings came FDA's proposed rule in 1997, June 4th, 1997, and this

proposed rule had a number of features including a limitation on the does which was less than 8 milligrams of ephedrine alkaloid per serving and it required certain label warning statements and conditions of use.

Considerable amounts of data and other information were presented at these public meetings and were placed in our public docket. This included information about products containing ephedrine alkaloids, the sources of the alkaloids, as you heard this morning, the known physiological and pharmacological effects of ephedrine alkaloids and finally the adverse effects of ephedrine alkaloids as derived both from the scientific literature as well as adverse event reporting.

What are the products that we are talking about today? There are a wide variety of ephedrine alkaloid-containing products. As you've heard from Dr. Fong, there are traditional medicines that use these, they are primarily for respiratory conditions and under the direct use health-care practitioner there are drugs both prescriptions and OTCs mainly for allergy, cough and cold preparations, as well as asthma. You have heard about the street drug alternative, but we're not talking about any of these type of products today. We are only talking about dietary supplements that contain

ephedrine alkaloids.

These products are widely sold in the United States. Almost all the products contain multiple ingredients. They are usually combined with other stimulants including caffeine. Sometimes yohimbine as well as vitamins and minerals, et cetera.

The primary uses that we see they are marketed for are weight loss and energy, fitness and bodybuilding, and a general category of other which may include four lung purposes et cetera.

This is just a picture showing the wider variety of products. We estimate that there are somewhere between 3 and 400 different types of products that are now on the market and again they fall into groups for weight loss and energy and ergogenic bodybuilding type products.

The sources of ephedrine alkaloid can be ephedra species or Ma Huang as Dr. Fong said, but other botanical sources are also possible. These include seta cordifolia, pinoyella; however, it is most common that extracts from botanicals are listed as the source of ephedrine alkaloids, and finally there can be synthetic sources of a these alkaloids.

The major alkaloids as you have heard from Dr. Fong are ephedra, pseudoephedrine, norephedrine,

methylephedrine, norpseudoephedrine and methylpseudoephedrine. The L forms are what occurs in nature in you don't see racemic mixtures or salts in nature.

The sources of our information come from a wide variety of areas. They come from medical practice. You heard Dr. Fong state that in traditional medicine there's been a these five centuries of use. In allopathic medicine the ephedrine alkaloids have been used at least 75 years now. There is a ever-growing medical scientific literature based on research done in the area and there is postmarketing surveillance. And in the case of dietary supplements containing ephedrine alkaloids this is voluntary reporting.

Along with the sources of evidence there are different types of evidence. These include the preclinical which are usually animal and in vitro and give us a mechanistic type of information to observational, epidemiological, and clinical trials. And clinical trials have kind of been the gold standard. But these are usually probably are usually the most infrequent. A well-controlled clinical trial usually has only several hundred patients in it, and is usually for a relatively short duration. So the most

information that we learned on possible adverse events occur in the postmarketing period where we use adverse event monitoring which would be considered a type of case reports.

And just for an example, a clinical trial to detect a relatively common adverse event, one occurring at 1 percent rate would require at least three to 500 patients to be able to reliably detect that. The clinical trials that are in the published literature now on ephedrine alkaloids for the most part do not have this many subjects in any of them.

As Dr. Fong mentioned we know a lot about the characteristics of ephedrine alkaloids. These are amphetamine-like sympathomimetic amines, they have direct and indirect effects, they primarily affect the cardiovascular and nervous system. The exact effects depend upon the alkaloid and I've already talked about the L forms.

The pharmacology and mechanism of action he also spoke about, but I am just going to quickly review. In the cardiovascular system it can cause basal constriction and cardiac stimulation, including increased contractility, increased heart rate, and increased stroke volume, central nervous system stimulation, and other effects including

bronchodilation and effects on skeletal and smooth muscle and various organs and glands.

From these known effects derived most of the adverse effects that we see associated with ephedrine alkaloids. So the adverse effects that we see affect predominantly the cardiovascular and the nervous system and in the cardiovascular system we have hypertension, angina, cardiac ischemia and infarction cardiomyopathy and cerebral vascular events including hemorrhage any infarction.

In the nervous system we have central stimulant effects as well as mania and psychosis seizures and I have drug abuse here but it should just be abuse, dependence, and addiction.

And finally there have been reports of myopathies, uropathies, including urinary retention, effects on the GI system, including vascular effects and dermatologic reactions.

This slide is a reminder just in what context do we evaluate dietary supplements? And it is really no different than other products that we look at. The considerations for use including the population, the pattern of use, and the type of products and ingredients. The population for these dietary supplements includes both the general population but

special subpopulations. The pattern of use include the amount, frequency, and duration, as well as particular conditions of use in which it may be used, including hard, physical exercise, caloric restriction, et cetera, and finally the type of products and ingredients. These are sympathomimetic amines that have known effects.

Further they are often combined with other stimulants ingredients which can cause an interactive or synergistic affect.

This is just to again compare and contrast what we know traditionally about ephedra to what we know in dietary supplements today. Historically ephedra was only considered a medicine. It with health-care practitioner prescribed, used predominantly for respiratory disorders; the formulation of herbs with health-care practitioner selected they were very defined herbal combinations that are different than the combinations that are used today, and the duration of use very short term. The current use of dietary supplements products in the U.S. is that these are dietary supplements; the consumer selects the products; they used for different purposes than had been previously used, including weight loss, energy, bodybuilding; the manufacturer selects the ingredients

and the combinations that are used which are again different than what had been used previously; and, finally the duration of use is undefined but can be prolonged.

Just to get us back to where we were on our little evolution of safety, from the proposed rule, GAO actually did a study and evaluated our use of the data for this proposed rule. And I'm sure that all of you have heard what has been said. There were many criticisms about the use of the data; but, what isn't heard is that GAO really did support FDA's use of the data for its reason. And I just want to quote for you "FDA based its proposed rule on numerous reports of adverse events associated with products thought to contain ephedrine alkaloids. It also used evidence from scientific literature indicating that ingestion of ephedra alkaloids adversely impacts some individuals.

The number and types of errors warranted FDA's consideration and steps to address safety issue. However," and there's their 'however' "we have concerns about the strength of some of the information FDA used to support to aspects of the proposed rule, the dosing level and the duration of use limits."

Besides this, they also indicated that we had not performed a causal analysis of individual adverse

events; that many of the cases lacked documentation; and that we did not have criteria to determine which event should be considered serious.

And believe me, we have heard these criticisms. So we are now to the point of this public meeting and we really want to talk about what has happened since the proposed rule. There have been a number of efforts. Certain states and industries have taken efforts concerning the dosage and instructions for use; there have been new articles in the medical scientific literature that impact on the safety these products; FDA has commissioned a number of outside expert scientific reviews to answer some of the questions with that were considered deficiencies by GAO; and, finally, we have had a continuing receipt and evaluation of spontaneous or voluntarily reported adverse events. And these too we have sought outside experts reviews besides the in-house review.

In the medical scientific literature there are many more articles, abstracts, monographs on the effects of ephedrine alkaloids available in this time frame. And this time the information is specific in some cases to the effects of dietary supplements or pseudoephedrine or alkaloids. We are seeing that other patterns of injury are emerging besides cardiovascular

and nervous system stimulant-related effects. And there is information on potential pathogenic mechanisms.

For these last two bullets, one of the things that have been of interest is the thought of abuse potential of these as well as the suggestion that there may be direct neurotoxicity in the central nervous system from use of these products.

There have been a number of published clinical investigations on ephedrine alkaloids. The first of these is the Yale PPA study which was a case-controlled study of persons 18 to 49 looking at the end point of hemorrhagic stroke in PPA. And this was a very large study that showed that there was any increased risk, particularly in products used for weight loss. This has been put in an FDA docket and will be the subject of a public meeting to address the issues that are specific to PPA.

In the ephedra botanical dietary supplement area, in 1999, in FASEB there was publication of an abstract from Columbia St. Luke's on a double-blind, randomized, placebo-controlled 8-week efficacy trial of a ma huang guarana containing-product in obesity. Sixty-seven people were randomized, only 48 completed. In this trial indicated while there appeared to be some

efficacy there also were adverse effects including hypertension and palpitations seen.

And, finally, recently Calman, et. al, in 2000 have published a study another double-blind, randomized, placebo-controlled eight-week trial of effect in obesity of an ephedrine, synepherin caffeine salicin product, but with only 30 test subjects and 30 controls.

I mentioned that we had commissioned a number of outside scientific and clinical reviews. One of these was by Dr. Enchiosa, that looked at the pharmacokinetics, pharmacodynamics properties in relative toxicities of botanical ephedra versus ephedrine alkaloids.

The question has always been that somehow the botanical sources are not as potent or don't cause the problems that the synthetic sources cause. And Dr. Enchiosa was able to look, because of the number of new publications that have addressed the issue directly of pharmacokinetics and pharmacodynamics of the dietary supplement product is that there really are no differences in these properties when you compare botanical sources or dietary supplements sources to synthetic products.

There was a study by Dr. Quib Ray, looking at

the use of ephedra in traditional Chinese medicine; and, again, it was commonly used short term under a health-care practitioner's practice, but, not used for the purposes of weight loss and energy.

And, finally, by Dr. Walker we had an assessment of the likely reporting rates of adverse events and dietary supplements containing ephedrine alkaloids. And from this review the conclusion was is that these were very much underreported and the reporting rate was probably far less than 1 percent.

In the interim of this time FDA has continued to receive adverse events. If you look at this cumulative events, his is by report day, these are all the other dietary supplements, these are ephedrine alkaloids containing dietary supplements. We have had a fairly consistent proportion about a 40 percent proportion of all our adverse events in dietary supplements have been due to those that are associated with ephedrine alkaloids.

This is looking at the data little bit differently, from 1997 to the current time, you can see the number of adverse events reported for ephedrine alkaloids containing dietary supplement year 2000. It is just through the first part of August, but if you calculated this out based on receipt today this number

would be somewhere in here. So, we are continuing to receive serious adverse events.

What's different about these adverse events? Well, we heard what GAO and others have said about the documentation, et cetera of these adverse events, so we have made very concerted efforts to get better documentation on these cases including additional FDA investigations that can give us information about how the consumer used the product, medical records, product labeling, and labeling. And then we have performed a number of in-depth clinical evaluations including in-house for the clinical research and review staff in the Center for Food Safety and Applied Nutrition, from our colleagues in the Center for Drug Evaluation and Research, and by a number of outside experts. These include Dr. Woosley, Dr. Benowitz, Dr. Ricaurte and Dr. Stolle.

And you will hear some of this, this morning.

What we did is say what was different about these cases and how should we study them. So we picked a time frame, and we picked June 1st, 1997, I have a typo there, 07. Which is very close to the time that we published the proposed rule. and we took it through a 22-month period so that we would have time to actually look at these so the cut off was March 31st,

1999, with any follow-up that could be received in-house by the end of December 1999. Typically it takes us anywhere from three to six months or longer to be able to investigate these adverse events and to get information that we need for evaluation.

There were at least 140 adverse events reported in this time on at least 143 consumers and we evaluated from demographic information, product use, clinical course, diagnoses, outcome, classification of adverse events, amount of documentation, and reason for using product.

This is our cut on these reports. Of the 140 reports we considered that eight were unevaluable. These were cases of multiple unidentified patients, cases where the event being reported we decided was not an adverse event, cases where we couldn't tell it the product with the dietary supplement or if it was a drug. In one case there was an incorrect temporal relationship and there was in one case there was confounding by the co-ingested product which was GBL.

The other cases we did an in-depth evaluation as I stated, and then screened these into not supporting of a causal relationship including those that had insufficient information to make assessments. They were 48 where the signs and symptoms were not

consistent with ephedrine alkaloids; there were nine cases where so many products had been used that it was impossible to ascribe any of the effects ephedrine alkaloids, there were two cases. Cases where there were too many confounding or complicating factors, 11; or cases of intentional misuse or abuse, there were two.

So this was 55 percent of our population. The other 45 percent we used a formal structured attribution analysis scheme that we could look at them and we divided these into attributable and supporting of a causal relationship.

Now, we've been asked many times what is the difference between association and attribution or causality? Well, association means there is really some link there and I'm using this quote from Dr. Hill from 1965, which is nine viewpoints as to whether association means causation. It doesn't mean causation automatically, and that's the strength of the association, the consistency of the association, the specificity of the association, temporality, the biological gradient, plausibility, coherence, experiment, and analogy.

I should mention also that there are many such schemes and there's really no consensus or no gold

standards on what is the best schema to use for adverse event monitoring whether its for spontaneous reports, voluntary reports, or that associated with clinical trials. This is what we did though, for attribution analysis, we checked the temporal relationship between the products use and the adverse event. We wanted to know if medical care had been sought for the adverse event and whether there was health-care professional attribution of the adverse event, whether there was evidence of dechallenge, i.e., the consumer got better when the product was discontinued, and if the symptoms -- signs ad symptoms came back when the person again took the product.

How the product was used. Was it used per direction or was it used, misused or abused? Were other products used at the time of the adverse event? What was the reason that they were using these products; were they weight loss, energy products, or were they bodybuilding products or were they others? Were the underlying conditions or product use a more likely explanation of the adverse event? This is looking at alternatives or alternates explanations, and finally, is the event consistent with the known affects of ephedrine alkaloids or likely extensions of the known physiological or pharmacological effects of

ephedrine alkaloids.

This was all done, as I said, with a very structured data form which is available in the docket as well as the individual results on each case. And these are the results that we see and this is from the full case series. Overall more adverse events are reported for women which could be expected since more of the products that we see all the weight loss and energy product. Although we are seen more adverse events being reported for men; 39.8 percent than we saw in our previous serious.

The age range again is mostly young adults; 64 percent of the injured persons were under 39 years of age; and 16 percent of the injured persons were 19 or younger.

When we evaluated consumer characteristics that may have impacted on the adverse event, we noted that most consumers reported that they use the product according to the directions on the label and labeling and most of them saw a health-care practitioner and the majority of them were temporally related closely temporally related to the use of the product.

In looking at duration of use there was a wide duration of use it ranged from under one day, or even on the first time of use on up to very chronic

use, and you see the spread; approximate 30 percent are associated with short-term use which we defined as less than or equal to one week meaning that 70 percent were longer-term use.

When we looked at the amounts of documentation that we have, a lot of adverse events are reported by consumers. And in fact if you look at just the flow of how they come into the center, you know, about a third of them come through our field investigators, a third come through Medwatch which are predominantly health-care professionals reporting, and a third come directly to the center. So, approximately 36 percent overall are from health-care professionals. In looking at all of the cases that we have evaluated, over 50 percent has some kind of additional information including medical records and many of them had copies of label and labeling.

We clinically classified the adverse events as we've done previously into serious cardiovascular, serious nervous system, and other adverse events. We also class them according to not serious or in cases that we couldn't tell as being unclear. The overwhelming majority of adverse events that we saw in this new case series were four serious adverse events. And this probably reflects a bias in reporting more

serious adverse events than less serious.

Cardiovascular system adverse events included myocardial infarction, ischemia, stroke, dysrhythmias and severe hypertension. And in this slide, the first slide that I am just showing the differences between the total group for serious cardiovascular adverse events and what I'm calling the attributable supporting; both groups would be attributable or supporting attribution; the group that had insufficient data to be able to further assess.

The serious nervous system effects included seizure, depression, psychoses, and addiction was also reported as an adverse event and was seen across all of these groups.

Other serious adverse events that weren't cardiovascular or nervous system included neuropathies, gastritis, hepatitis, rebnomyallises, and a case of nephrogenic diabetes insipidus.

We also evaluated whether certain product use factors could impact on the adverse event. One of the first things we noticed is that men and women use the products for different reported uses. And I think this could be expected, but many more of the women use it for weight loss and the men use it for fitness bodybuilding purposes.

However, when you look at the classification of adverse events by gender you also note that there's a different pattern based on gender. In women you have many more cardiovascular adverse events, whereas in mean you have more nervous system adverse events.

And if you further subset this, looking at serious adverse events just in the men, but by use, in looking at the weight loss category it's really very similar to what you see in women, in that the cardiovascular system is what is predominantly involved. But in the fitness group you have a very high proportion of nervous system type of facts.

It appeared that strenuous exercise besides possibly being involved with this group also impacted on a cardiovascular adverse events in that we had at least seven reports of serious cardiovascular adverse events that were associated with strenuous exercise.

In addition to looking at all of the other information, we in the interminable and supporting cases, looked at all the information that was available on the product label and labeling, and all of these contained information on how to use the product including the dose frequency and durations. Almost all of them contained warnings or precautionary statements. Many stated the actions that consumers should take in

the event of an adverse event, and all were multi-ingredient products. The overwhelming majority of these had caffeine and other sources of stimulants in them.

Again I said that we specifically looked at the likelihood of association in the subset where we could evaluate that; and all of them are temporally related because that was, of course, a criteria, and in a very high proportion of them there is health-care attribution that the adverse event was caused or contributed to from the use of the ephedrine alkaloid containing products.

The majority of these were for weight loss purposes. And almost all of the consumers improve when the product was discontinued indicating positive dechallenge. In much smaller proportion of them there was evidence of positive rechallenge.

Looking at other alternative explanations for the adverse event, you know, a very high proportion of these consumers used other dietary supplements and other medications at the same time that they were using a dietary supplement product containing ephedrine alkaloids.

Furthermore, many of them had certain types of underlying health conditions. However, it was the

opinion of the clinical reviewers that these other factors, the usr of dietary supplements other medication use or the underlying health condition was not a more likely explanation of the adverse event. And the dietary supplements containing ephedrine alkaloids were thought clinically to have caused or contributed to the adverse event in all these cases.

And, finally, we evaluated whether the observed signs and symptoms were consistent with the effects of ephedrine alkaloids and/or were likely extension of their pharmacological activity. And again we had a very high rate where there was agreement.

So just to briefly summarize, the current FDA data are consistent with the scientific literature concerning the effects of ephedrine alkaloids, and previous information from adverse events. These adverse events can be predicted from the known physiological and pharmacological actions of ephedrine alkaloids and, therefore, should be anticipated if consumers are going to be using these products.

FDA believes that the current availability and use of dietary supplements containing ephedrine alkaloids continues to be a serious public health concern, but we are here in a listening mode. All along in all of our evaluations and presentations at

public meetings we have been very open in soliciting any information that could be available to impact on our evaluation and assessment of safety. And we're hoping we hear some today, thank you.

[Applause.]

DR. BIETZ: Dr. Jones, panel members and guests, this morning I will present an analysis of adverse event reports for ephedrine alkaloid containing dietary supplements.

DR. JONES: F the record, Julie, please identify yourself.

DR. BIETZ: I'm sorry?

DR. JONES: Give your name -- just for the record, for the recorded record.

DR. BIETZ: Oh, certainly. My name is Julie Bietz, I'm with FDA CEDER, Office of Postmarketing Drug Risk Assessment.

I will present an analysis of the adverse events that were conducted by CEDER's office of postmarketing drug risk assessments this past February and the complete review document that we prepared is available for public inspection under Docket No. 00N 1200.

CFSAN provided our office with the following materials for review; adverse event reports that were

received by CFSAN on 139 cases from June of 1997 through March of 1999. As you've heard CFSAN conducted extensive follow-up investigations to obtain additional information on many of these cases, and this information was made available to us for our review.

In addition, CFSAN provided us with summary tabulations of 1,176 adverse event reports that they received from 1990 through November 1999. These tabulations included some demographic information, but only limited clinical information. The above-mentioned 139 cases are included among these reports.

The remainder of the presentation will focus on the clinical review of the 139 cases. Thirty-one cases were excluded from further review for the following reasons: 11 cases were confounded by the concurrent use of other products that may have attributed to the event. In nine cases it was not possible to ascertain whether an EADS product had been used. There were six consumer reports of events that were not readily evaluable. Three cases were confounded by an underlying disease, and in two reports several individuals were named but no unique consumer could be identified. This left 108 cases.

The median age of these 108 remaining cases was 35 years with a range of six days to 67 years.

More cases involved women than men. Most cases involved the cardiovascular system or central nervous system. There were 49 hospitalizations or emergency room visits reported and there were nine deaths.

At least 45 different EADS products were identified among the 108 cases. Most were combination products that also contained caffeine from a variety of sources. Most individuals reported taking the EADS product as directed without apparent misuse or overuse.

Given the amount of information contained in the reports, it was not possible to estimate either a daily EADS dose or the ephedrine alkaloid content of the products that we found in these reports.

Forty-six cases reported cardiovascular events. The median age of these cases was 39 years with a range of 15 to 64 years. More cases occurred in women than in men. All cases were reported to have occurred during the use of an EADS product. Seventeen cases were report within one week of product use with the range of one does to over one year of product use.

In 30 cases the EADS product was being used weight reduction. Hospitalization occurred in roughly two-thirds of cases and there were seven deaths reported from cardiothoracic arrest, sudden cardiac death, or stroke. Both health-care providers and

consumers reported these events in roughly equal numbers.

Cardiovascular events included cardiac arrest, cerebral vascular events including stroke, cardiac ischemia, hypertensive events, and cardiac rhythm disturbances. This table shows how the 46 cardiovascular events were categorized and the number of cases within each category that appear to have no known risk factors. Overall one-half of cases had no known risk factors such as an underlying illness or concurrent use of another product that could have contributed to the event.

The age range for the 41 central nervous system cases was 15, I'm sorry -- central nervous system conditions included central stimulant events, psychiatric events with or without central stimulant effects and seizures. This table shows how the 41 central nervous system events were categorized and the number of cases within each category that appear to have no known risk factors.

Again, overall one-half of cases had no known risk factors such as underlying illness or concurrent use of another product that could have contributed to the event.

The age range for the 41 central nervous

system cases was 15 to 51 years. More cases occurred in women than in men. The onset of central stimulant effects were shortest with longer durations of use reported for psychiatric events and for seizures. The EADS products were predominantly used for weight lost or as enhancers for bodybuilding. Unlike cardiovascular events hospitalization was reported less frequently and there were no deaths reported. More central nervous system events were reported by consumers than health-care providers.

The remaining events included gastrointestinal, musculoskeletal, renal and hematologic events. This table shows how these events were categorized and the number of cases within each category that appear to have no known risk factors.

Roughly 40 percent of these cases had no known risk factors such as an underlying illness or concurrent use of another product that could have contributed to the event.

So in summary then, CEDER conducted an in-depth review of 139 cases that had been reported to CFSAN between June of 1997 and March of 1999. In general, these cases describe young adults, particularly women, who were using EADS product for weight loss. Cardiovascular and central nervous system

adverse events were most common. Based on information available roughly one-half of the cases had no known risk factors such as underlying illness or concurrent use of other products.

An association with EADS products with these adverse events as strongly suggested, given the presence of ephedrine alkaloids in all products evaluated in this review. The similarity between these events and the known pharmacological events of ephedrine alkaloids, the close temporal proximity of EADS product use and adverse events that were reported, and the absence of known risk factors in half the cases.

In addition pre-existing risk factors may have played a role such as hypertension, such as a prior history of hypertension or cardiac arrhythmia; may have played a role in some of the more series events the were reported; and a voluntary nature of adverse event reporting implies that the actual number of events occurring in the general population would be higher.

DR. JONES: Is Dr. Ricaurte here?

DR. RICAURTE: Dr. Jones, members of the panel, ladies and gentlemen, good morning. My name is George Ricaurte. I am an associate professor of

neurology at the Johns Hopkins University School of Medicine where I direct movement disorders clinics on the Bayview campus and where I also direct a research laboratory on neurotoxicology.

I am a board certified neurologist and I hold a Ph.D. in pharmacology. I have conducted research on the neurotoxicity of amphetamine and related substances for greater than 15 years.

Today I will be address points one, two, and four of the ephedra questions predefined by the Office of Public Health and Science of the U.S. Department of Health and Human Services for today's discussion.

To avoid confusion, I would like to begin with a definition of terms. As shown on the first slide, ephedra as I will be using the term today is meant to refer to plant derive material containing ephedrine and related alkaloids. These include ephedrine, pseudoephedrine, norephedrine and methylephedrine.

As I believe has been discussed previously by Dr. Fong, ephedrine is generally regarded as the main active ingredient in ephedra, although there are also other active substances. Ephedrine, as has been mentioned, is known to exist in four stereo isomeric forms in two corresponding racemic mixtures.

Structurally and pharmacologically ephedrine is best characterized as a sympathomimetic amine. Other sympathomimetic amines shown on this slide include dopamine, norepinephrine, epinephrine, phenylpropanolamine, and ephedra. Like those of other sympathomimetic amines the effects of ephedra are those that would be predicted to occur following stimulation of the central and sympathetic nervous systems, either directly or indirectly. To varying degrees sympathomimetic amines typically produce increased mental arousal, increased sense of well-being, increased heart rate and blood pressure, vasoconstriction, cardiac stimulation, bronchial dilatation, and decreased appetite.

Depending on the particular circumstances a number of these effects might be considered positive and indeed have been exploited medically over a number of years, but usually with due regard for adverse effects.

Adverse effects of ephedrine alkaloids generally, although not always, represent an exaggeration of their milder pharmacological effects and may include sleep disturbance and anxiety, agitation, mania, psychoses, drug dependence, hypertension, stroke, seizures, cardiac arrhythmia,

myocardial infarction, and excessive weight loss or anorexia.

These adverse effects are typically seen in individuals who take excessive doses of ephedra, but can also occur in some individuals who use ephedra-containing products as directed.

Clearly adverse effects of ephedra alkaloids can be serious and indeed fatal. While very little is known about the potential influence of gender, race, or ethnicity, and the risk of developing serious complications of ephedra-containing compounds there are several population that appear to be at increased risk. These shown on this slide and include populations with certain neuropsychiatric disorders and those with significant cardiovascular disease. The latter would include people with -- individuals with hypertension, coronary arteries disease, occult or known aneurysms, or arterial venous malformations, and possibly obese subjects since these individuals are more likely to suffer from atherosclerotic vascular disease.

Persons with a family, or family history of anxiety mood disorder may also be at higher risk for developing neuropsychiatric complications of ephedra. Finally, it is possible that individuals with a history of drug dependence are more likely to abuse ephedra-

containing products.

Ironically, the very same group of individuals that are targeted for use of ephedra-containing products are often those at highest risk for developing serious complications. For example, deconditioned, overweight individuals would be expected to be more most susceptible to the cardio and cerebral vascular complications of ephedra. This may also may be true for individuals who are engaged in vigorous activity since exercise itself increases sympathetic tone.

Unfortunately, very little controlled research has been conducted regarding risk associated with long-term use of ephedra by these groups of individuals. Similarly little is known about the propensity for individuals to develop tolerance to the effects of ephedra. This too is unfortunate because with the development of tolerance escalating doses are the rule, and high doses are more likely to lead to more serious complications.

Thus far I have detailed some of the adverse cardiovascular and neuropsychiatric effects of ephedra that can potentially occur. I will now devote the remainder of my time to a less well-known and more insidious potential adverse effect of ephedrine, CNS

neuro injury or neurotoxicity.

As indicated previously ephedrine is the most abundant and the main active ingredient in ephedra. As shown on the next slide, ephedrine is closely related and structured to another sympathomimetic amine, methamphetamine shown on the right. As you know, methamphetamine is a well-known drug of abuse.

In addition to the remarkable similarities and structure ephedrine and methamphetamine have two other similarities and I would like to bring to your attention. First, and I must confess, contrary to my initial expectation when I first considered the structure of ephedrine which unlike methamphetamine has a hydroxyl group which is somewhat difficult to see, but it's a hydroxyl group that's located on the beta carbon of the molecule, a moiety that one might anticipate would interfere with the crossing of ephedrine through the blood brain barrier.

Based on that structural difference, it was my initial impression that in ephedrine would be largely devoid of central effects. As I alluded to earlier this expectation of mine -- initial expectation of mine proved incorrect. This is perhaps best illustrated in an early study of Martin and colleagues where they looked at the physiologic and subjective and

behavioral effects of a number of amphetamines derivatives including ephedrine and methamphetamine.

Somewhat to my surprise, what these investigators showed in this early study which, as you can see, was published in 1971 what these investigators found is that -- an I'm afraid you don't see the upper portion of the panel, but methamphetamine is shown here in the open circles, ephedrine are the open squares. And having to find this slide if you could move down just a tad I'd appreciate it. Because what this is intended to show you it is that once you account for the difference in potency between methamphetamine and ephedrine by simply increasing the dose, the efficacy of these two sympathomimetic amine's in this case in raising blood pressure is nearly equal.

The second interesting and important observation from this early study was that as was the case with the sympathomimetic effect of ephedrine with regard to the psycho stimulant affect once you adjusted for differences and potency, again by increasing the dose of ephedra, the psycho stimulant effect of ephedrine was indeed comparable to that of methamphetamine.

The other similarities between ephedrine and methamphetamine that I would like to bring to your

attention today has to do with potential of these two compounds to produce brain dopaminergic neurotoxicity.

Research carried out in various laboratories over the last two decades or so has yielded very strong evidence that methamphetamine has the potential to damage brain dopamine neurons. Dopamine neurons as you may be aware are neurons that originate in the substantial nigra shows schematically here at the level of the brain stem, and from there these nerve cells send axon projections to primarily to the striatum, a region of the brain involved with estral paramedial mobile function.

These are the nerve cells that degenerate in Parkinson's disease indeed is the degeneration of these nerve cells in Parkinson's disease that accounts for the movement disturbance that patients with Parkinson's disease experiences.

Before presenting to you some recent data that we collected on the neurotoxic potential of ephedrine I would like to briefly summarize for you what we already know about the neurotoxic potential of methamphetamine. Hopefully this will help place the ephedrine neurotoxicity data in its proper context.

As shown on this slide there are a number of indicators that methamphetamine has the potential to

damage brain dopamine neurons. In summary the evidence for methamphetamine neurotoxicity comes from both chemical and anatomic studies. The chemical studies indicate that a number of unique markers for brain dopamine axon terminals are markedly reduced in animals with previously administered doses of methamphetamine.

The anatomical evidence or structural evidence indicates that the loss of these dopamine axonal markers, the long-term loss of these dopamine axonal markers is due to degeneration of dopamine axon and axons terminals.

Notably the toxic effect of methamphetamine is highly selective since it does not involve noradonergic, cholinergic neurons, gabaergic neurons, or other neurons thus far analyzed. With the single exception certain of seratononic neurons which are affected in some species.

The next few slides depict representative data on methamphetamine induced dopamine neurotoxicity in animals collected in my laboratory. In these studies baboons were given various doses of methamphetamine ranging from .5 milligrams per kilogram up to 2 milligrams per kilogram. These doses were given systemically at two-hour intervals, a total four doses were given. The animals were then allowed a two-

week drug-free period so that we might measure long-term toxic effects of methamphetamine as opposed to acute pharmacological effects of the drug.

Two weeks after treatment we measured a number using postmortem tissue from these animals; specifically striatae tissue, we measured dopamine, dopa, as well as the dopamine transporter here labeled with a compound called Win35428 and the vesicular monoamine transporter here labeled with a dihydro -- attriated dyhydrotetabenazine. Regardless of which are these dopamine axonal markers we measured, as you can see here in the data before you, what you can see is that there is a dose-related reduction in each of these axonal markers that's produced by methamphetamine in the baboons striatum. Notably, even the lowest dose that we tested produced significant effects.

Collectively the chemical, an as I will show you in a second, the anatomic data that we and other laboratories have collected, collectively that data strongly indicates that methamphetamine has the potential to damage dopamine axons and axon terminal is shown schematically here. And it is that damage or destruction of these terminals that leads to loss of dopamine in the various other dopaminergic axonal markers.

The toxicity of methamphetamine can be detected with imaging techniques as well. Shown here are the results of two different types of imaging studies carried out in the same baboons that I just showed you the neurochemical data from.

In other words, after -- bear with me here for a minute because this is a somewhat complicated but important slide. There are three panels, the top, the middle, an the bottom. Just focus on the middle and the top. The middle simply represents a postmortem quantitative autoradiographic study where we are now using tritiated label when to label the dopamine transporter the control animal is shown on the left, the methamphetamine treated animal is shown on the right, and you can see essentially what you saw with the chemical data. And that is, that there is a profound loss of dopamine transporters in the striatum of the methamphetamine treated animal.

Now, please focus on the top panel. What's important and I think interesting about this panel is that these are the results of a study carried out with carbon 11 labeled Win35428. As you may know carbon 11 emits positrons and thus permits the execution of positron emission tomographic studies. These are elegant studies that allow for direct visualization of

dopamine terminals at the levels of the striatum.

DR. JONES: Dr. Ricaurte, you have about 30 seconds. So if you would move towards a summary and conclusion.

DR. RICAURTE: Very good. And what you see simply here is that during life this animal shows loss of dopamine transporters that is confirmed in postmortem studies. Armed with that information with PET imaging, what we've done is conducted a study of human methamphetamine users, compared them to controls, and to patients with Parkinson's disease and you can see that the human subjects previously exposed to methamphetamine shows evidence of loss of dopamine transporters.

What does this have to do with ephedra? To directly compare the neurotoxic potential of ephedrine with that of methamphetamine, we have recently done some studies in squirrel monkeys, where monkeys are given fivefold higher doses of ephedrine to accommodate for the difference and potency. And what this slide simply shows you is that ephedrine like methamphetamine produces a loss of dopamine transporters -- of dopamine and dopamine transporters.

In summary, what I've covered today are, I've discussed the cardiovascular and neuropsychiatric

complications of ephedrine-containing products, their abuse liability, I've touched upon, and I've also discussed the potential for neurotoxicity. Due to limitations of time, I cannot address some of the limitations that I recognize are in our animal studies. But the reason for presenting them today is to simply highlight for you the neurotoxic potential that ephedrine has for dopamine neurons in the brain. Thank you.

DR. JONES: Thank you, Dr. Ricaurte. We would invite you to put the full text of your remarks into the record. We would welcome full text.

[Applause.]

DR. RICAURTE: I will. I will then submit a complete record of the written remarks, thank you.

DR. JONES: Very good, thank you.

Dr. Woosley.

DR. WOOLSEY: Dr. Jones, members the committee, and guests, I am, as shown here, Raymond Woosley, Professor of Pharmacology and Medicine at Georgetown University where I am chair of the pharmacology department. I have a Ph.D. in pharmacology. I am also board certified internist and board certified clinical pharmacologist, and currently president of the American Society for Clinical

Pharmacology and Therapeutics.

I am a consultant for the FDA, a special government employee, working with CFSAN for the last few years, but today I appear as an unpaid volunteer for presenting to you this information today.

I have no financial ties to any other products involved and hope that I can give you an objective analysis of the 140 cases that were presented to me about a year so ago.

I will be giving you my opinion of those cases. Dr. Neil Benowitz, a clinical pharmacologist also and colleague performed a similar analysis and came to the same results. I think though, as I have watched the other presentations of those same cases, it is interesting that in 140 cases that were very complex it's always there are differences between the different approaches that people take. And I will today give you my approach based on the following background or biases however you want to look at them; but my experiences.

My experience began as a clinical pharmacologist 25 years ago studying the variable factors that contributed to the response of drugs trying to identify those factors which would explain variability. Often studying drug action, many times studying, unfortunately, drug toxicity.

I was co-director of the cardiac arrhythmia suppression trial. This was a trial that ended in 1988. It was the study of drugs intended to save lives, but the study was stopped prematurely because the antiarrhythmic drugs under study actually were taking lives. And that began my interest in cardiac toxicity.

It was heightened in 1990 when I saw a case of seldane-induced sudden cardiac arrest and began a series studies often with funding from the NIH and the FDA to study the factors responsible for that fairly rare cardiac complication. So in reviewing -- actually in 1995, 95 cases of medwatch reports of ephedrine products that had been reported to the FDA, and the 140 cages that I have more recently reviewed, it was heavily influenced by my experiences with the cardiac drugs in the antiarrhythmic trials and the cardiac actions of antihistamines and many other classes of drugs over this period of time.

So I guess in those cases we were looking at the medwatch reports often of prescription drugs where we often knew some of the pharmacology, but not all of it. And in this case, it is very different. We are looking at the pharmacology or cases where the pharmacology has been known for centuries. And we are

looking at the drug in a different use than its usual prescription use. So it is a different situation and people come at this with different backgrounds and different approaches.

But I used the following scoring system. I said -- I went through the cases and gave them a score of one to five. And five was used when the reaction reported is generally accepted as a medical consequence of the sympathomimetic amines, such as ephedrine, it was temporally related to the administration of the product or the report included a dechallenge with resolution of the symptoms associated with discontinuation of the product, and the product contained the information necessary, and the report contained the information necessary for a reasonable evaluation of causation excluding other likely causes. So that would get a score of five, or would be very similar to the reactions generally expected, it was temporally related, but the report may have lacked dechallenge or some of the information necessary for a reasonable evaluation.

So it was a slight reduction in the amount of evidence that was available in the report. And as was said earlier, unlike the reports in 1995, these included intensive evaluation, affidavits from

witnesses, family members, and sometimes victims or people injured in the report.

A score of three was that it was generally accepted as a medical consequence, but there lacked a great deal of the information necessary for complete evaluation of causation.

Two, there may have been other cases or other causes that might have explained it. And a score of one, that the report was just too incomplete to allow one to reasonably assess the report.

And causation in my case was assessed by view of copies of the medical records, affidavits of the patients and their family members, analytical chemistry reports which were often available of the biological fluids in ephedrine-containing products and postmortem reports.

Well, in doing this, I was heavily influenced by many of the structures that you have already seen, and I will go quickly through these because you've seen this already. But I think it is important to repeat that in analyzing these reports you have to -- I had to take into account all that I had learned about the pharmacology of sympathomimetic amines. And the structural similarities between ephedrine and amphetamine is shown here; the simple difference of a

methyl group and hydroxyl group here.

Methamphetamine was talked about a second ago. The very similar chemical structure, the fact that phenylpropanolamine is also a metabolite of ephedrine. It's pseudoephedrine is chemically very similar but by changing the stereochemistry to pick an isomer that has all the same properties but a different sensitivity, a different dose response curve.

The message that I got from looking at all of this is that all of these compounds can do the same thing but at different doses and different sensitivities, different potencies, sorry. And of course they were acting as adrenaline often does because it is a catecholamine which has the same phenelylamine backbone which allows it to interact with alpha and beta receptors and stimulate the sympathetic nervous system. And there are products on the market like the phenylephrine which can constrict blood vessels and have medical use.

Well, these stimulant amines will affect the heart and blood vessels, increase blood pressure, and increase cardiac work and when any of these compounds have been looked at including, ephedrine carefully over the centuries, and in more recent years in clinical reports those sympathomimetic amines are known to be

associated with stroke, heart attack, arrhythmias, and sudden death.

So this was known, and I used that fact in analyzing the under 140 cases. And if you look at the 104 cases of the 140 that I've scored as four five you find that the fives are shown here, the fours are shown here, there were seven cases that I felt that there was very strong evidence that the sudden death was caused by or associated with the use of an ephedrine-containing product. Three were rated as a four. Arrhythmia such as atrofibulation, ventricular tachycardia, palpitations to arrhythmias and cardiac awareness, syncope, dizziness, chest pain, and myocardial infarction were all seen. These are the effects that you would expect with any sympathomimetic amine given to a large population of people.

And the brain stimulate affect would be expected for this class of compounds to lower the seizure threshold, to cause psychoses and cause anxiety and other CNS symptoms. And when I reviewed the 140 cases I found that five -- that I gave a score of five to ten cases of seizures, tremors occurred in seven, personality change one of the most frequent reports that I gave a score of five, 24 cases, and a score of four was given to four cases here.

Severely increased blood pressure, six were given a five, and there were 12 severe strokes that I felt were clearly associated and probably the result of the use of an ephedrine-containing product.

Well, what are the factors which caused these kinds of events to occur? I think clearly dosage can be involved, but in almost all the cases, in fact all the cases that I reviewed, dosage was not a factor. These drugs were -- and I said "drugs" as Harry Fong said earlier over and over, these are drugs and the drug dosage for these compounds was as recommended on the labeling. So dosage can't explain all of this. And I think one of the things that we've learned with terfenadine and many drugs now, is that there is receptor diversity. We know that there are ion channels in the heart, for example, that a simple change of one amino acid in the protein can alter the sensitivity to a drug. And that mutation or that polymorphism in a receptor or an ion channel can be responsible for an untoward response supersensitivity to this kind of drug.

So, I believe that what we know about the receptor diversity and the receptor polymorphism that existed, beta receptors and ion channels are enough to explain the exaggerated cardiovascular response that

are occurring in many individuals.

At the same time many individuals can take these compounds and never have a serious reaction. It is this receptor diversity that I believe is responsible for this disconnect, where some people can tolerate these products without any problem, but an occasional person will have a stroke or heart attack.

Why is ephedrine not in use in medicine today? Well, there are more safe and effective drugs that are available. And medicine has moved past a drug, as Harry Fong said earlier, only a two -- a therapeutic index of only two. We now have many other products with therapeutic tendencies of 10 and 20 which can be used clinically and not cause reactions in the supersensitive population that is out there today.

So I conclude that ephedrine, although safe for some healthy people, causes stroke, heart attack, seizures, sudden death, and other less serious adverse effects in susceptible individuals, or a normal people giving excessive dosages.

I think the warning labels will not be effective in preventing the harmful effect of ephedrine because the individuals often do not know that he or she is susceptible to the adverse effects of ephedrine until they take their first few doses. And for me

there is no acceptably safe dosage of ephedrine when used as a dietary supplement, because, it has no proven nutritional or even medical value using current standards of evidence to offset its known harmful effects, adverse effects, expected to occur in some people. So to me the risk benefit ratio is just unacceptable. Thank you.

[Applause.]

MS. CULMO: My name is Cynthia Culmo. I am employed by the Texas Department of Health, but I am here today on behalf of the Association of Food Drug Officials who has paid for my travel expenses to this meeting.

In light of the time, and my nervousness, I'm going to speak fast so I should get through in plenty of time. I am here to present a state's regulatory perspective on this issue. I don't have a lot of impressive credentials, but now I have a the unsolicited long-term on-the-job knowledge and experience with this category of products.

I'll give you a background on the Association of Food Drug Officials, herein referred to as AFDO, and I am pleased to offer comments on this important issue.

AFDO is a 104-year-old organization that represents federal, state, and local government,

regulatory officials, and industry associates. Many of whom are involved in food safety efforts focusing on dietary supplements. AFDO strongly supports the Food and Drug Administration's desire to develop strategies for achieving effective regulation of dietary supplements.

AFDO wishes to comment on a few of these and more specifically on the issues of this docket. We had consistently, through testimony and in numerous written comments, placed a high priority on product safety and provision of adequate label information to help educate the consumers on safe and appropriate use of dietary supplements.

Although the safety of dietary supplements is often equated to conventional foods, many contained concentrated extracts of botanicals that have profound physiological and pharmacological affects that result in added health risk when compared to conventional foods and the whole unextracted botanical.

AFDO continues to support fast tracking of specific good manufacturing practices, particularly those requirements that address critical safety areas related to consistency and purity of the ingredients and dosage. This is particularly important for all dietary supplements.

On several occasions AFDO has expressed its concern regarding deficiencies and the labeling information for safe use; including information regarding contraindications, problematic drug or product interactions, and restrictions for which safety has not been established by clinical studies or historical uses in at-risk preparations such as young people.

Today's docket addresses the safety of dietary supplements containing ephedrine alkaloids. The traditional medical use of these products, the use of the products as dietary supplements labeled for weight loss and exercise enhancement, and the known physiologic and pharmacological actions of ephedrine alkaloids, including their use in combination with other stimulants.

The following are responses to the specific questions posed for this forum with regard to additional AERs and the information that was made public by the FDA this past spring. In regards to the first question -- and I am not going to read the questions -- the known and expected physiological actions of ephedrine are well-documented, as you have heard the previous speakers allude to. The beneficial actions include bronchial dilation and decongestant

effects. Another positive action might be weight loss and overweight or obese persons due to appetite suppression and thermogenesis.

Serious adverse physiological actions are also expected and known for this potent stimulant including cardiovascular neurologic and other types of serious adverse events that have included elevated blood pressure, cardiac arrhythmias, heart attacks, seizures, stroke, psychosis and death.

Not surprisingly, each of these adverse events is represented in the AERs, reported to the FDA and several states. Since all the products in the reports contain ephedrine and since all the adverse events are consistent with ephedrine toxicity, there is clearly and association between the use of dietary supplements containing ephedrine alkaloids and the adverse events.

And just as in the first serious of AERs reported by FDA in 1997, this new series documents that over 90 percent of the injured consumers took the ephedrine-containing dietary supplement products as recommended, or at lesser amounts, than as directed by the manufacturer on the labeling.

Not to go over each of the external reviewers as well as CFSAN and CEDER there was an evaluation

performed by mention -- and I apologize if I mispronounce names -- an RPH and MS, Claudia Kowalski, a PharmD within the FDA's Center for Drug Evaluation and Research, CEDER, who describe the adverse events as possibly related to the use of ephedrine alkaloid-containing products.

CEDER's division of Drug Risk Evaluations' more conservative evaluation may reflect its traditional frame of reference in evaluating adverse reactions from prescription drugs where well-controlled clinical trials have established the drug safety effectiveness, contraindications, and most likely tbe adverse effects. It also reflects their expectations that physicians familiar with the patient's medical history prescribed the drugs and report the adverse events through a well-established system.

Dr. Janet Woodcock summarized CEDER's report as follows, and I quote: "we nonetheless believe it is most likely that ephedrine alkaloid-containing dietary supplements, EADSs are causing these adverse effects. The primary reason for our belief is" -- she lists, one, and two. I'll quote three: "the similarity between the adverse events and the known pharmaco dynamic properties of ephedrine alkaloids."

Additionally although many EADes may contain

other ingredients the most cogent interpretation of these data focuses on the common element, the presence of ephedrine alkaloids. In other words, the fact that the adverse events are associated with ephedrine alkaloids containing a variety of other constituents, taken with the fact that we are not at the same level of adverse events associated with the other constituents on the EADes, it supports the causal relationship between ephedrine alkaloids and the adverse events.

Under question two, DSHEA, the Dietary Supplement Health and Education Act, dietary supplements or more regulated as foods rather than the stricter regulatory requirements of drugs. And they are intended to supplement the diet to affect or maintain normal structure and function of the body or produced general well-being.

The central nervous system stimulation of ephedrine alkaloids may play a role in suppressing appetite and increasing perceived energy levels. An increased metabolism produced by ephedrine particularly in combination with caffeine, it may increase the rate of weight loss for individuals on a low-calorie diet.

These effects are drug effects, and there are significant risks associated with taking the products

for energy or weight loss, particularly when use for long periods of time. The bronchodilation and the cardiovascular stimulation produced by ephedrine alkaloids had no role in maintaining normal structure, function, or well-being in healthy individuals.

Dr. Wei from the School of Medicine expressed that ephedra is used in its traditional Chinese medicine, TCM, for short-term treatment of medical conditions such as cough, nasal congestion, asthma, emphysema, and bronchitis. These conditions are either diseases or characteristics of diseases in dietary supplements and are not intended to diagnose, treat, cure, or prevent any disease. Ephedra is not used in TCM to lose weight, pump iron, or to fight fatigue.

Considering dose and duration studies have demonstrated that obese women on a low-calorie diet taking 20 milligrams of ephedra, three times a day, with or without 200 milligrams of caffeine for six months experienced increased weight loss compared with women taking the placebo.

We are not aware of data evaluating lower doses of ephedrine for weight loss or data characterizing the effective dose and the duration of use for ephedrine for increasing energy or bodybuilding. The question addresses efficacy and not

safety.

The states health departments, pharmacies and agricultural departments, as well as the FDA, have long been concerned with the safety aspect of ephedrine alkaloid-containing dietary supplements. Both state programs and AFDO have testified to this concern. During comment periods in public hearings, representatives of industries have promised to publish in peer review journals the results of on going, double-blind, placebo studies that will show that ephedrine-containing dietary supplement products were safe.

The promises were sometimes delivered at the eleventh hour and have been instrumental in delaying passage of any restrictions to improve safety by the regulatory agencies on more than one occasion.

Six years have passed and the touted safety studies still haven't been produced. What happened?

The financial cost of a large clinical trial to determine safety should not pose a burden for manufacturers that claim billion dollars in sales for ephedrine-containing diet products alone. Have the studies suffered due to the small numbers of subjects, the short duration of the studies, or the number of subjects that dropped out or were eliminated due to

significant side effects? If the studies participants were subjects that were screened in as healthy individuals to be part of a carefully controlled physician-monitored, clinical study, what were the reasons for noncompletion of those studies?

It appears that the studies, to the extent that they lasted, document the pattern and the types of adverse events reported and known for sympathomimetic stimulant agents even among apparently healthy persons.

Dr. Woosley so adequately summarized in his review of the adverse events a great deal of discussion and deliberation has sought to identify a safe dose of ephedrine in dietary supplements. However, a safe dose assumes that there is safe medical value to taking ephedra as a dietary supplement. The lack of proven medical benefit of dietary supplements containing ephedrine alkaloids makes the risk benefit ratio these supplements unfavorable.

The occurrence of serious side effects makes the use of ephedrine-containing products as a dietary supplement at dosages they can increase the blood pressure and heart rates in susceptible individuals unacceptable without medical supervision.

The adverse events reported to FDA in a series and in a previous series on dietary supplements

containing ephedrine alkaloids, represent only the tip of the iceberg of the number of adverse events occurring from these products.

The evaluation by Dr. Walker, M.D. PhD of Harvard School of Public Health, concluded less than one percent of the serious adverse events caused by dietary supplements is reported to the FDA. The true proportion may well be smaller by an order of magnitude or more.

In the 20 months from June 1, 1997, to March 31, 1999, FDA received 140 reports of adverse events; 60 of which could be clearly attributed to ephedrine-containing dietary supplements, or supported a role of ephedrine in producing these adverse events.

Adverse events included deaths, permanent disabilities from cerebral vascular disruption, cardiac arrest, heart attacks, seizures and psychosis. If Dr. Walkers estimates of reporting rates are correct, 300 to 3,000 or more individuals a month may be suffering serious, and in some cases, disabling or fatal adverse events from dietary supplements containing ephedrine alkaloids. Risk from dietary supplements containing ephedrine alkaloids are serious, and the consequence is are devastating for some affected individuals and their families.

Are the outcomes associated with the use of these products affected by dosage? Outcomes may be affected by dosage. Data currently available indicates the dosage of products currently marketed for weight loss of bodybuilding and enhancing energy propose a significant risk of life-threatening adverse events. But these data do not indicate an expected safe dose.

In addition, over half of the members of an advisory expert panel convened by the FDA in 1996, the Food Advisory Committee concluded that based upon the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements.

The growing number and the consistency of the AERs associated with dietary supplements containing ephedrine alkaloids and the continued lack of safety data must lead one to the same conclusion today.

Mario Enchioso, from Newark Medical College stated in his conclusions in his review, "I believe that these relationships are of importance in relation to whether one can identify a safe dose of ephedrine for supplements.

In the absence of clinical indication that would provide some basis for risk to benefit consideration, it would not be possible to recommend a safe dose of ephedrine considering user

characteristics. Strenuous to moderate exercise appears to increase the risk of serious adverse effects from dietary supplements containing ephedrine alkaloids in both men and women."

Dr. Benowitz commented, "several individuals in our view suffered adverse events during exercise. Exercise results in activation of the sympathic nervous system which increases blood pressure and heart rate. Ephedrine and/or caffeine could augment the cardiovascular stress of exercise which could be another mechanism for difference in the individual's susceptibility."

He also concluded that the three types of the adverse events reported in a AERs he reviewed were consistent with the known stimulant properties of ephedrine and caffeine.

In addition, it is well-established that the combination of stimulants has a synergistic effect with increased risk for adverse events.

As Dr. Love noted, it could have a potentially positive impact on thermogenesis that may also account for the increased adverse effects seen with a combination of these agents.

Another negative result documented with taking ephedrine-containing dietary supplement products

is a positive urine screen for amphetamines. This could be particularly problematic for athletes and military personnel. Most amateur collegiate, and professional organizations now prohibit the use of ephedrine-containing products by their athletes.

Serious adverse effects from dietary supplements containing ephedrine and these AERs, the last series of the AERs and the AERs reported to the states occurred from the first day of use to after months or years of use.

Safety of these products cannot be assured by limiting use to days or weeks. Life-threatening adverse events occurred in young individuals with no identified, preexisting medical conditions. Label warnings directed to individuals at increased risk because of medication or medical conditions would not protect these individuals.

The states and the FDA have ample evidence why these products are being consumed for weight loss, performance enhancers, and energy boosters. This is easily demonstrated by FDA's review of the products and other marketing advertising and labeling received by the states. An example of the consumers' perception of these products is exemplified in petitions received during Texas Department of Health's rule-making

procedures that said sign up today, save the Chinese speed, and please sign to keep the Chinese speed.

It's virtually impossible for an individual state to bring about meaningful restrictions on sales or labeling these nationally distributed products. And many states have delayed individual action because they are expecting and waiting for FDA to provide leadership and finally act with meaningful restrictions.

DR. JONES: Could you please wrap up or get to a conclusion?

MS. CULMO: Okay. I need to wrap up here.

In conclusion, being a representative of many involved or regulatory oversight, I am compelled to address the regulation of these products. AFDO encourages the FDA to act expeditiously.

There have been two included advisory committee reports, two series of external reports, scientific medical specialties have been utilized, and most have concluded that dietary supplements containing ephedrine alkaloids present significant or unreasonable risk of injury or illness under conditions recommended by the manufacturers.

It's time to place to politics and the money aside and act responsibly as the public health agency relied upon by the general public to protect their

safety. Recent polls demonstrates that FDA is held in high regard by the general public and is viewed as doing a good job.

To continue that trust FDA must act in these needless injuries. We would like to thank the USPHS for this opportunity to comment, and we look forward to working with all interested parties to address this important public health issue. Thank you.

DR. JONES: Thank you, Ms. Culmo.

[Applause.]

DR. JONES: And thank you to all panel members for staying on time even if I needed to prod a couple times.

We want to open for questions and answers first from the panel. I will take the prerogative, since I have a microphone, of asking the first just of the panel, do any of you have any data whatsoever on the role of the thyroid as an underlying condition since an estimated 20 -- some say as many as 40 percent of women from about midlife to later might have an undiagnosed thyroid condition which obviously can have cardiac and other effects. Any suggestions of the role that that might contribute as the underlying conditions and interaction with these compounds?

DR. WOOSLEY: I think clearly the hypothyroid

individuals are known to be at increased risk for sympathomimetic amine administration. I don't recall in 140 cases if there were any. I seem to call that there were, made Lori knows, but hypothyroidism is also a potential complication in that these people are at increased risk of arrhythmias as are the hyperthyroid.

So, I think we don't have data that I'm aware of to quantify that group any more than we have any other group. But we would, based on the pharmacology, based on the disease itself or the illness, I would say that those would be another group that often are unaware of their condition who might be at increased risk.

The other aspect of it is, there were some of these cases that were taking thyroid supplements and if that dosage wasn't adjusted perfectly at the time they took the sympathomimetic amine that could be another risk factor.

DR. JONES: Thank you. Dr. Coates.

DR. COATES: Thanks very much. I have --

DR. JONES: For the record, Paul, would you state your name?

DR. COATES: I'm Paul Coates, from the Office of Dietary Supplements at NIH. I have two questions -- brief questions for Dr. Love, and one brief question

for Dr. Ricaurte.

Dr. Love would you -- maybe I missed it but would you be able to provide the references for the St. Luke's Roosevelt study and for the Calman study which you referenced on your slide? You noted that the St. Luke's Roosevelt study was in abstract form, do you know if it's been published since?

DR. LOVE: I have not heard that it's been published. It was published in abstract form in FASEB in 1999.

DR. COATES: And the Calman study?

DR. LOVE: The Calman study, I forget the journal it was just recently published in 2000.

DR. COATES: And then I wonder whether -- the number were going by fast before me. I was concerned to be sure that I understood that the adverse event reporting system represented, was there a difference between the adverse event reports that occurred among those who were using the products primarily for weight loss as opposed to those who was using the products primarily for bodybuilding for want of a better term?

DR. LOVE: From our data more men, of course, appeared to be using it for the fitness bodybuilding purposes. An in that population looking at the classification of adverse events there were more

central nervous system type of effects. Particularly if you looked at it there were more cases of seizures in some of these individuals, but also strenuous exercise did impact on just the cardiovascular events that that you could see irrespective of what the product was used for.

DR. COATES: And if you do not mind I will ask one question of Dr. Ricaurte. Dr. Ricaurte, you provided a tantalizing approach towards the end when you said that the methamphetamine studies on dopaminergic neurons in the baboon could be reflected in similar studies in humans and then you ended with the tantalizing brief remark about ephedrine studies and monkeys. Can you give me a little bit more insight into how you think that the studies that were done in monkeys could draw you to the same conclusion that you had about methamphetamine in the baboon and in the human?

DR. RICAURTE: Well, as you know, the closing remarks were not meant to be so tantalizing brief and I apologize. I think the data on the neurotoxic potential of ephedrine compared to that of the methamphetamine although it is at a very early stage; there is a paucity of studies.

That data clearly indicates to me that like

methamphetamine, ephedrine -- this is the minus isomer of ephedrine, that ephedrine has the potential to damage dopamine neurons in the primate central nervous system.

I think that that's where we are with the current studies. What we don't know as yet is, what are the lowest doses of ephedrine that produce the neurotoxicity in the primate brain. We don't know whether or not the data in monkeys extrapolates to humans.

With the methamphetamine subjects I can tell that when you look at issues of dosage, the doses that produce the toxicity in nonhuman primates are on the orders of those used by some humans. We don't know if that's also the case for ephedrine.

DR. JONES: I have questions, two more questions from the panel, Dr. Schwetz and then Dr. Lieberman.

DR. SCHWETZ: Berne Schwetz from the FDA. I have a question for Dr. Woosley. How much of an adjustment is normally made to account for the tolerance that develops? And are these adjustments more likely or less likely to be made by people who would have the receptor to polymorphism?

DR. WOOSLEY: It is an excellent question and