one that I'm not aware of good data on. Clearly there is tolerance to some of the cardiovascular effects and we know with other drugs that people titrate their dose to maintain a drug effect. And I think that it also raises the other concern, and that is variability between products. Because if you titrate your dose to a higher level because of the tolerance and then you change lots or you change products, and now you're taking in an ephedrine product that has two to three times higher dose, then that could be a very dangerous situation.

But Dr. Ricaurte may be able to answer it better about the CNS effects. But the cardiovascular effects of these compounds, there is tolerance that develops, but there is a sustained stimulation of the heart and the blood pressure if the dose is increased. And I think those are the cases where -- I mean, we all exercise and the blood pressure and the heart rate goes up, but we don't maintain that high blood pressure and high heart rate throughout the day and the hours, and the heart and the body has a chance to rest.

Whereas, in this case when your ingesting the products continually for days, then I think that's putting people who might have small -- aneurysm or some other predisposing factor bringing out a problem that

would not have otherwise occurred

DR. JONES: Last question from the panel Dr. Lieberman.

DR. LIEBERMAN: Dr. Lieberman, U.S. Army Research Institute of Environmental Medicine, I have a two-part question for Dr. Woosley and Dr. Love. The question is, given your concerns about ephedrine and ephedrine-like products in dietary supplements, do you have similar concerns about these products when they are sold as OTC decongestants? And the part of the question is for Dr. Love is, is there any surveillance data that speaks to that particular situation issue?

DR. LOVE: Well, again, as I talked about the types of products we were talking about today, the issue of the effects in OTC products were really off the table because the are regulated under a different scheme than the food products. So we were trying to focus this just specifically on the effects in these dietary supplement products. I am not from the Center on Drugs and I don't think that I am confident to comment on anything they may have in this area.

DR. LIEBERMAN: I understand that those products are regulated very differently. But my question had to do with the data that might be available from those products, not a generic question

about your opinion on whether they should be regulated differently.

DR. LOVE: We have asked them to do reviews in the past and there has been limited information available in their database or adverse events or these type products. Remember the products contain very different ingredients than the dietary supplement products.

DR. WOOSLEY: I would say that, yes, I do have the same concern, but less because there is a risk benefit ratio that you can assess. I mean, there is pharmacological effect that a drug is being used with an informed label, it's been reviewed by the FDA as a drug, and there is a medical value to it, some response, the reason a person keeps taking it and they realize that benefit. So there is a risk benefit ratio that can come from that.

I would also say though, that if you look at pharmacology of the heart and blood vessels beta-blockers reduce death. And anything that stimulates the sympathetic nervous system is probably the wrong dose or the wrong individual going to cause cardiovascular harm. So I think you should assume that any central -- any cardiovascular stimulate will have some harm if used in a broad population. The question

is, is it being used under the proper supervision and inform the public and with some medical value.

DR. JONES: Thank you. Let me turn now to questions from the floor. You have been very patient. There are microphones on the floor, and if you would identify yourselves just for the record so that we have that, and then keep your question brief so that we can accommodate all who like to ask. Dr. McLaughlin.

DR. MCLAUGHLIN: Jerry McLaughlin from Nature Sunshine Products. I have three questions. The first relates to the therapeutic index of the ephedrine. I learned a long time ago that you can't believe everything that Harry Fong says. And saying that a therapeutic index of three exists for the ephedrine is way off, and then to have it reduced to two, and one of the later speeches was way off too. I challenge you to back that up, and the University of Michigan we learned that the therapeutic index is the effective dose 50 divided by the lethal dose 50. Find those calculations I have my Merck index I could certainly help figure that out right now.

The second thing is, no one is reporting on the total number of people who are using the ephedra products from which you are extracting these adverse effect reports. What is that number? I've heard it

quoted on 20/20 by someone from the American Herbal Products Association that it is approximately 2 billion doses a year, something like that. I suspect that's probably close relating to the amount of products that we sell. Two billion doses a year, I'm not quite sure how many how many people are taking those 2 billion doses a year, but I suspect considering that 54 percent of Americans are obese or overweight, at least, and that a lot of those people need to take something to try and take the curb off their appetite and reduce their risk of death from the associated diseases. I suspect that we are looking at probably a population of 20 million people that may be taking ephedra products.

And what are you telling us? That there are 1,100 reports in the last ten years of adverse effects of 20 million people. Let's look a some of the other things that use all the time like polio vaccine in which there are ten people that get polio or one million people that get the vaccine.

Some antibiotics like chlorophenol, one person of 200,000 dies of aplastic anemia that takes chlorophenocol. So the total instances of these adverse effects is very small when you look at the overall population. And all the reports today neglected that. And then finally, on the report about

the baboons getting their dopaminergic neurons damaged, I couldn't help but notice the dose. Even the lowest dose that was given to the baboons of methamphetamine was 5 milligrams per kilo. The dose of methamphetamine itself when taken for diet is 5 milligrams per 70 kilogram person. Okay. So even your lowest dose is like 70 times -- it was .5? Okay.

So seven times then. So your lowest dose was seven times the usual dose. Now, you said okay there are some people who do take more than that. But I am going to point out to the audience, and the people listening, that those are the abusers who are tolerant to methamphetamine.

DR. RICAURTE: Let me address very quickly because this was in the latter part of the -- there are two points with regard to the issue of dose. It wasn't 5, .5 milligrams per kilogram. When you consider issues of dose, there are two very important adjustments that one has to make. One is an adjustment for difference in body mass using principles of interspecies drug scaling. Once you do those adjustments the .5 milligram per kilogram dose becomes low on a milligram per kilogram basis for the human being. So you need to make that adjustment.

The second point I would make is that for the

ephedrine, we don't as yet know, indeed for methamphetamine, we haven't fully defined the lowest dose that produces the brain dopamine or toxicity. So at this point I just think we are at too early a stage to draw conclusions about -- such as have been drawn that the doses in humans are much, much lower than those that produce neurotoxic effects on animals.

I just don't think at this point that we know.

DR. JONES: Any other responses from this panel to Dr. McLaughlin's questions.

DR. LOVE: Well, I think his comment on reporting rate is correct one, but it goes both ways. We do not have information where we can do incidence and prevalence. We do not have access to the information that we could provide that. Yes we have enumerator and we know that that is massively underreported, but we have no information on a denominator; and knowing the members of doses does not help us with that.

DR. McLAUGHLIN: I'll give you some information tomorrow.

DR. JONES: Dr. Woosley.

DR. WOOSLEY: I would like to address the therapeutic index issue, because therapeutic index

implies that there's a per therapeutic value, and it's impossible to calculate a therapeutic index until someone shows a proven value of these products. We know that there is underreporting at the Agency in the safety databases. In order to really calculate the incidence as Lori just alluded to, you would need another approach to do that; and one of the ways that the Agency has always evaluated these types of products is to ask them to do large enough control trials to give you a risk benefit ratio to document benefit, and then give you a careful assessment of the harm.

If there are 2 or 3 billion people taking doses of these products, the society deserves a control trial to answer these questions and I don't think we should be guessing or extrapolating from animal baths and animal tissues when people are taking these drugs.

DR. JONES: Thank you, Dr. Woosley. Ms. Culmo.

MS. CULMO: Can I quickly address the denominator issue? Industry consistently relates this denominator of 2 to 3 billion servings sold. He just alluded to the fact that he could give her data tomorrow. It will be on servings sold. There is not information on actual denominators consumed. We have a number of reports where consumers have reported that

they have taken the product one time and had to discontinue the product because of adverse effects. So there is not a known denominator at this time.

DR. JONES: Thank you. Yes, sir.

MR. SIEGNER: My name is West Siegner, a partner with the law firm of Hyman, Phelps and McNamara and I am here on behalf of industry. First I would like to address partially the question that Dr. Lieberman raised about OTC use and side effects. I don't, I can offer this as a quote from the record of the '96 advisory committee meeting and can provide the quote, I may not get the words exactly correct but this issue of adverse events with the OTC database came up repeatedly at that meeting and at one point someone from the Center for Drug Evaluation Research and I believe it was Dr. Wyntrob, got up and addressed that issue and stated something to the effect that we have no significant adverse effects in the database from labeled use of the products. And, again, I would be happy to provide that to panel.

Another issue that I wanted to raise simply because this afternoon we'll hear more information on background risk and consumption rates, and I think this is important to put everything into perspective. The Center for Drug Evaluation and Research from FDA

submitted a written evaluation of the adverse events to the docket and this is in the docket. And I think it is important to have this in the record this morning and I will just read the quote conclusion from their report. It's not the only conclusion but it is one of conclusions. "It is possible that the reported serious adverse events are of coincidental background spontaneous occurrences in the population and are not necessarily causally related to ephedra products uses. The availability of additional information including product, market or usage data would be useful to the further characterization of the potential risks associated with the use of these products."

And then finally this is a point, Dr. Jones, you mention at the beginning that everybody is supposed to mention any potential conflicts. I am not questioning anybody's objectivity here, but I think it is important if the industry members are going to be required to divulge information on potential conflicts as I feel is appropriate, that everybody do that. And I commend Cynthia Culmo for doing that.

DR. JONES: We have asked people. Dr. Woosley did as well. I'm not sure Dr. Ricaurte did. But I am sure he would be happy to state for the record what his conflicts are. Those of us who are public

employees are public property and, you know --

[Laughter.]

MR. SIEGNER: I understand that. Thank you.

DR. JONES: Thank you though Mr. Siegner.

Dr. Ricaurte, do you want to state briefly any potential, you know, who has funded, where you've gotten funding et cetera, please record.

DR. RICAURTE: I, to my knowledge, do not have any potential conflicts interest and I have so indicated in this forum.

DR. JONES: Funding even from government to support your research?

DR. RICAURTE: All of funding for my studies at John Hopkins comes directly from the NIH.

DR. JONES: Very good. Okay. We are running close to lunch time but I do see three gentleman with questions, so I will take those questions. And then would ask if you do indeed have further questions, concerns, or comments that we can't get to in subsequent sessions, you know, for any of you who are here for those, we have some -- I believe there are some forms that are available for pickup you can raise those questions or express those comments to the record in writing and we would invite you to do so.

This gentleman, yes, sir.

MR. REINHART: People for pure foods. I wanted to ask two questions; the first one, Dr. Woosley would you comment on the pathophysiology of the punitive cardiomyopathies that you reviewed? Was there anything either dominant or consistent about the pathophysiology?

DR. WOOSLEY: The cardiomyopathies that are in the literature are those associated with sympathomimetic amines in general. The cases that I reviewed I don't recall any microscopic anatomy of the heart that would address your question.

MR REINHART: And second question for Dr. Ricaurte. Is the dopaminergic neurotoxicity associated with the depletion of norepinephrine.

DR. RICAURTE: No it is not. That's one of the really quite remarkable features of the toxic effects of these amphetamine derivatives because on the one hand, as you've heard, people will argue that the doses are high, although I'm not sure that that is accurate. But a remarkable feature of the toxicity is that it is extremely selective as evidenced by the fact that noradgeneric neurons are totally unaffected.

MR. REINHART: Do you have an insight as to what the mechanism of the toxicity is?

DR. RICAURTE: It's been a tough nut to

crack, but I think the weight of the evidence right now would suggest a primary role of endogenous dopamine that perhaps dopamine mediates a cytotoxic effect of methamphetamine and related substances.

MR. REINHART: Thank you.

DR. JONES: Thank you. Let me take the second question from here since this microphone hasn't gotten much.

MR. GREEN: I am Ralph Green. I am an attorney, but I am not with any governmental agency or any other agency. But a quick question, I think, for Dr. Woosley, or anyone else on the panel. What is the percentage of gastrointestinal problems that had been exhibited by the ephedrine in your analysis of the 140 cases or any other studies that you might be aware of?

DR. LOVE: I don't think there is data that can give you a percentage. There are case reports in the published literature on the effects of ephedrine alkaloids on the GI system we have noted them in our studies as well as Dr. Bytes has noted them. There are a range of adverse effects they can be seen in the GI system including those that could be due to the vasculature of the GI system.

MR. GREEN: Of the 140, Dr. Woosley, that you studied, were there any gastrointestinal problems among

that group of people?

DR. WOOSLEY: I do recall there were some, but I did not quantify them I focused mostly on cardiac and neurologic, but I do seem to recall that there were some. But, again, I don't think there's any way to, with a percentage in a spontaneous system.

DR. JONES: Thank you. Yes, sir.

MR. LAFABI: Hi, I am Bob Lafabi. I am a professor of public health for sports medicine at Armstrong State University in Savannah, and I am also a consultant for Twinlab.

It was a great series of information. I think we'll appreciate that it seems very reasonable, very sound but I got to tell you, I just keep having this question, you know, where's the beef? I expected to hear a lot about AERs. I mean, let's face it, there may not be 2 million dosages every year but I can tell you, in terms of number of uses we are in the hundreds of thousands, and I expected to hear hundreds if not thousands of AERs. What we've got here in this brief review was 60 possible AERs, possible, 46 and 41 from CFSAN and then a theory over neurotoxicity, reasonable, but a theory, an analysis of those same AERs and then opinions from another regulatory agency.

When you look at -- let's take a very

conservative figure, 600,000 users, very conservative.

DR. JONES: Thank you. Get to the question please.

MR. LAFABI: I'm sorry?

DR. JONES: Get to the question, please.

MR. LAFABI: The question is, how can anyone look at providing this kind of information to the FDA in its docket that would enable it to or give it some support for limiting something where there's no data. By the time you take out artifact, the fact that many of these people may have been taking illegal drugs that they did not tell you about, and then they didn't know that they had risk factors that you obviously don't know about, you may have absolutely nothing left. And so the question is, where is the data, the real data?

DR. RICAURTE: Let me just answer with a brief statement -- a sentence. I think the concluding sentence of my presentation -- I'll get it in somehow, in this regard, I say, I find it puzzling that while on the one federal policy in the United States severely restricts access to methamphetamine and other related drugs. On the other hand, current law provides various at-risk populations unlimited access to ephedrine alkaloids. I think you can't ignore the pharmacology of the these substance. And therein would lie my

rationale as to why a careful look at these products is in order and why some oversight is needed in order to simply not allow unlimited access to a methamphetamine analog.

DR. JONES: And to your question, sir -- oh, Ray go ahead.

DR. WOOSLEY: I was just going to say, I think it was said earlier, we have been pleading with the industry to provide the safety data that we all need. The pharmacology is very consistent, the reports are very consistent, this is not an issue of whether people are being killed or harmed by this compound; the question is, is there any medical value to them being exposed to this known risk and the systems that we have available will never quantify that risk, but they have identified it and there's absolutely no doubt by reasonable people that there is harm.

I think we need the data that this gentleman has called for and I hope the industry that is selling this million/billions of doses will be responsible and provide us with that data.

DR. JONES: And clearly that was exactly what I was going to say, the question stands on the record, sir, and we acknowledge it indeed as a call for more data. We have voluntary adverse event reporting

system, and, you know, in God we trust all others bring data. And what we brought to you today is what we have in the adverse event reporting system, and have recognized the imperfections that that system brings with it. There is a lot more work that does need to be done. We acknowledge your question, it is a valid question, we would like to see more work done.

I will acknowledge now, we are at lunchtime and I would indeed like to start on time at 1:10 p.m. Thank you all very much for your in put.

[Whereupon, at 12:12 p.m. the meeting was recessed to be reconvened this same day at 1:10 p.m.]

A F T E R N O O N S E S S I O N

[Time noted: 1:10 p.m.]

DR. JONES: Welcome back folks. Let me note for our 1:10 p.m. panel, Adverse Event Reports, this ephedrine education panel of experts review. There will be a change in order of the presenters, so if you would simply note this, Dr. Kimmel will go first then Dr. Page, then Dr. Karch, then Dr. Farber, then Dr. Hutchins, then Dr. Olney, and, finally, Dr. Adams.

Thank you, Dr. Kimmel, go ahead.

DR. KIMMEL: Thank you, Dr. Jones, ladies and gentlemen of the panel, and members of the audience. My name is Steven Kimmel from the University of Pennsylvania, School of Medicine, Department of Medicine Cardiovascular Division. The Center for Clinical Epidemiology and Biostatistics in the Department of Biostatistics in Epidemiology.

I have been funded by the Ephedra Education Council for this meeting including travel.

I will put up some relevant background and talk over it in the interest of time. I am the chair of a multidisciplinary panel of experts sponsored by the Ephedra Education Council who were charged to review and assess the scientific information relevant to dietary supplements containing ephedrine alkaloids.

The other panel members will introduce themselves as they step of the present.

Prior to a July 27 meeting, each panel reviewed the health assessments that the FDA released on April 3rd including health assessments prepared by consultants to the FDA. The panel also reviewed the relevant published literature, and reviewed the adverse event reports. The literature review included the published literature on the incidence of heart attacks, strokes, and seizures in the general population of norephadra users, including young adults. And finally at our July 27th meeting the pane reviewed some unpublished data on the effectiveness of ephedra products in weight management.

Here is relevant background I have a masters in epidemiology and I do research in the cardiac affects of noncardiac drugs.

So, as an overview of what I like to talk about, there are three things: one, to address questions that ar raised for this meeting by DHHS, Office on Women's Health; second to discuss very briefly the phenylpropanolamine and hemorrhagic stroke case control study which I know was of interest to this meeting; and, third to relate other consensus statements reached by our panel.

So the first questions raised by DHHS. The primary question that we addressed was, does the available information show an association between the use of dietary supplements containing ephedrine alkaloids -- and I'll use the term "ephedrine" just for simplicity -- and serious adverse events when used as directed?

Other questions that we addressed, are there circumstances for which there are indications for dietary supplements containing ephedrine, and thirdly, are outcomes associated with user characteristics?

Turning now to the first and primary question is there an association between the dietary supplements and serious adverse events?

As you heard today the preexisting data consists almost exclusively to adverse event reports for dietary supplements. The panel also consider other data including physiology data primarily for over-the-counter ephedrine, pharmacology data primarily for over-the-counter ephedrine, pharmacology data, similarly for over-the-counter ephedrine, pathology data and other literature, primarily again for over-the-counter ephedrine alkaloids. And others will address these issues as the present.

I'm going to focus on the adverse event

reports. In addition we had available additional data which were sales data from a sample of ephedrine dietary manufacturers to use to estimate the incidence of serious events among ephedrine dietary supplement users. And to compare this to the background incidence of serious events in the population that as similar as we could find compared to dietary supplements users.

As you know there are many limitations to adverse event reporting. The primary one is that causality usually cannot be proven because there is no comparison control group. In addition, even associations dan be wrong. The reason for this is pretty straightforward. Events may simply be due to background risk. That is, they may have happened anyway. and even if the event is rare with enough users there will be events that occur that are unrelated to exposure.

In addition there are other confounding issues that make interpretations difficult. The presence of obesity, exercise as examples, which we know increase the risk of cardiovascular events are difficult to dissect from other factors including use of dietary supplements.

As a result of all this, the incidence rates are unknown which is important both for comparative

purposes" and for estimates of absolute risk.

In addition changes in adverse event reporting are difficult to interpret for many reasons. An increase in adverse unit reporting can be real, a real increase in events, it could be due to publicity which may be due to no real increase event if you get an increase in minor events. I'm talking now about serious events minor events reported for you owe you get events that were reported long ago, so in other words, your annual numbers really have not increased, y get reports of people who didn't even use the product, you get reports of people who didn't really have side effects. And the publicity as a marker for increased reporting, particularly of minor events has been documented in the literature.

And thirdly, you may have simply an increase in number of users. That is, you may not have a true increase in risk the risk being the number of events over the number of users.

This is a slide of the number of adverse event reports by the year that they were reported to FDA from 1993 to 1999. And the things that we noted here are first of all that rapid rise here in 1994, it comes down little bit, a dramatic rise in 1996 which comes down again and levels off quite dramatically

after 1996. So what is the reason for this? Is this an epidemic of ephedrine serious adverse events?

Well, I mentioned one issue which is publicity. This is not meant to be a proof slide, but certainly we know what was happening around this time. In 1994 formula one was receiving a tremendous amount of press, right before this. In 1996 FDA had to their press release on ephedrine dietary supplements; Montel Williams had a broadcast and there were numerous other events that certainly increased public knowledge of what was going on.

So some of these increases certainly could be due to reporting; again, certainly not a definitive analysis. The other interesting thing here, as I mentioned, was that the numbers come down the numbers of events come dramatically down here and we don't see a rise -- dramatic rise or we don't see it continue to rise. This would still be concerting, of course, if the number users decreased; if these reports scare people away from these products and decreased use, this was still be worrisome.

In fact, this is actually the opposite of what we see is happening. And now superimposed on the same yellow line is a new white line which is the estimated servings sold based on a survey I'll discuss

in more detail later. But suffice it to say that the number of millions of serving sold based on a survey of a small sample of dietary supplements manufacturers has increased dramatically in the years.

If dietary supplements increased the risk of serious adverse events and if reporting rates didn't change, and we know that there has been continued media attention in 1997, the FDA released their report in the Federal Register and that received a fair amount of media coverage. We don't see the blip here. So assuming that the reporting rates are the same the divergence of these curves is inconsistent at least with true association.

So in summary the limitations of spontaneous reporting are that they can't prove incidence rates. Effects of publicity are difficult to discern. There is nonspecificity of reports over reporting and, of course, underreporting, which you've heard a lot about, is always a concern and there's no control group.

So in order to try to address some of these limitations, and using data from sales of ephedrine dietary supplements, the panel had two goals. One was to try to estimate the risk of serious adverse events occurring among ephedrine users, and, second, to compare these with population-based estimates of risk

of the same events.

I'm going to focus on strokes, heart attacks, MIs, and seizures.

Well, what do you need to calculate incidence rates? You need the number of events and the amount of exposure we're going to usee in time.

Our goal was, if anything, to try to overestimate risk among users. As you'll see, all of these calculations have a lot of assumptions associated with them. We were trying to, if anything, overestimate risk, try to be as -- if you want to use the term -- "conservative as possible".

I will point out some of those as we go along. So number of events is the first thing we need and for this we used all events reported to FDA from June 1, 1997 through March 31, 1999. We included all of their events, whether they were attributable, supporting, or insufficient data. We assumed that they all really occurred and that they occurred on exposure to ephedrine.

Some specifics about these. For our MIs we included unstable angina and all sudden death in which MI could not be excluded. This is important because of the population-based statistics exclude these patients. They are based on hospitalized patients who survive to

come to the hospital. So, again, if anything, I think will be overestimating risk in ephedra users relative to the population statistics. And similarly for stroke we included all subtypes of strokes, not all studies do, and TIAs which most studies do not; other studies.

What are reporting rates? These are some data from the literature. These are from medications and looking at the series of events that we'll be discussing. In one study reporting rates for MI among a group of drugs was 2.4 percent; seizures in another group was 25 to 37 percent. Now, this was after vaccines at time of heightened awareness of adverse events and probably is a little high. Cardiac arrest, 18 percent. Again, in this study the physicians were aware that there was active surveillance going on so again it may be high.

But this is a range for the types of serious adverse events that we are looking at. These are studies of medications not dietary supplements and various medications were vaccines.

The reality is, it is impossible to know for sure what the reporting rate is. Specific to ephedra, we may see increased reporting because of mass publicity, the fact that these are severe events that are unusual in a younger population, and, therefore are

less likely to be attributable to other common causes; acute and occurred in close temple relation to the exposure -- these are not latent effects that occur five years down the line. We may see decrease reporting because of underreporting of dietary supplement events in general. This has been hypothesized -- some suggestions based on some surveys in the literature there's no, as far as I'm aware direct study of literature looking at dietary supplement reporting rates; and of course different reporting mechanisms to the pharmaceutical industry which reports adverse events to drugs is not available here.

Now, you know, which way this is going to go is unclear. I want to make one comment though related to Dr. Walker's statement in which heard about this one percent or less reporting rate. If you read his report carefully you'll see a could of things. Number one, he was not talking about ephedra. He was talking about all dietary supplements in general. Number, two, he acknowledges that all of these things might increase report rates. He acknowledges that these may decrease reporting rates too. But essentially, the 1 percent was for all dietary supplements and it was a guess.

And the basis for that guess was a guess. A

the only example that was given in that paper was L-tryptophan which as, you may know caused use and aphelia myalgia syndrome in which Dr. Walker was concerned that there was underreporting. If you read the FDA report in the Journal of the American Medical Association and follow up to that, essentially tragedy, they calculate the 50 percent of all serious events reported. And if you included minor events it was 25 percent; certainly not 1 percent.

So the 1 percent is a guess, I think, based on other data. We may use that as a lower risk and we do.

So for our calculation we used reporting rates of 10 percent. And we used this based on the at the time what we had which was what the FDA used in the Federal Register on ephedra alkaloids in 1997 for some calculations.

We did, however, look at a range, 1 to 20 percent to see how sensitive our estimates were.

Okay. That's the enumerator. What about the denominator of exposure time? Well, as I mentioned, there was an independent survey which was commissioned by the American Herbal Products Association and performed by one with Arthur Andersen. This was an anonymous survey of 42 companies, of whom, only 13,

that is 31 percent reported on annual sales.

From the annual sales data we calculated an estimate of the number of person time exposed. We are going to assume again to be conservative that this, these 13 companies, are the only companies that sell ephedra in the entire country.

Okay. This is clearly a worst-case estimate in terms of exposure time which will increase our risk. We also assume that perhaps this represented 75 percent. We could have said 60 percent. We really were just trying to see how sensitive our estimates were to our assumptions.

So we have all the members in place we have the number of events adjusted for reporting proportion and the persons years of ephedrine use in this same time frame.

I want to turn now to the first event. Next slide. No, wait, I don't want to turn to the nest slide.

We wanted to compare this to the background risk. In order to do this we performed a comprehension literature review of epidemiology studies of population-based statistics and tried to identify a range of risk from U.S. studies representing a similar age range a reported cases. There are some issues with

this there's difficulties, I will try to point those out as I go along.

Now the first event. Seizure rates. Assuming in a 10 percent reporting rate and assume in the sales from these 13 companies that responded were all sales, we estimated 2 million person years of exposure; this is in a 22-month period. This is not one year this is 22-month period in which the AERs were reported. We calculated an estimated rate of seizures at 3.6 per 100,000. This is below the background rate in the population of the 20 to 60 per hundred thousand -- population statistics.

I am in no way saying that ephedra reduces the risk of seizures at all. All I am saying is that the estimated rate is certainly not consistent with the dramatic increase in rate.

This slide here shows the estimate of seizure rate per 100,000 person years with changes in our estimated reporting percentage as well as changing usage of ephedra products. The yellow line here is assuming all the companies that reported are the only manufacturers, the 10 percent is our baseline risk; and as you can see, as the reporting rate drops down to 1 percent obviously the estimated seizure rate goes up, but is still certainly consistent with the range of

events here.

The next is stroke rate. Our estimated rate of strokes among ephedra users 7.1 per 100,000 the background rate was three to 60 depending on the study.

This slide shows how those estimates have changed by reporting rates and consumption used. For almost all of our assumptions they are within range. There's one here that's a little bit and I want to make two remarks here. One, this is a wide range in the population, I'm sorry, I didn't say in the last slide, this gray box is the population rate. So it goes from 5 to 60. It is very hard to sort of get an actual number; 40 percent of all strokes in AERs that we looked at occurred in women over the age of 45, The five here is from studies of women under the age of 45 who belong to HMOs. So along with the healthy worker effect is essentially a younger population.

We know that in a population of 45- to 50-year-olds the strokes rate goes up dramatically, it's 50 to 100 per 100,000. We use 60 as an upper limit, again, realizing that this is really all just estimates.

The second point I want to point out is that we're not comparing one rate to another rate, we are really just looking at a range. It's impossible to say

what the actual number is. We are looking for a consistency with the reported range or with the population range and we're also looking for dramatic differences. And I'll give you just one example, when Fen-Phen -- at the time Fen-Phen was removed from the market or Fenflordamine and textrafenfloamine, rather, the estimated prevalence of valve abnormalities, and this was a different situation because this was distinct pathology, but the incidence of the prevalence of valve abnormalities was 30 percent based on case servings.

The population-based prevalence was 1 percent. So the concern was that there was 30-fold increased risk and we're looking for that kind of dramatic risk here realizing that we have a range, and we don't see that.

Turning now to myocardial infarction our estimated rate was 5.1 per 100,000, again, consistent with the lower rate in the population. This is that same study of young women here,

And again as we very our assumptions the numbers change, but, again, most of the numbers are certainly consistent with the range. Rhe other thing I will mention again is that these MI studies were all from people under the age 45, and 30 percent of the MIs

that we saw in the reports were over the age of 45. And if you take those out, these dots here will come down. So it's quite hard to compare.

And in fact it is hard to compare. There are numerous limitations to this. We had to make numerous assumptions to obtain our incidence upsets estimates. We tried to vary it over a reasonable range and we tried to be conservative. This not a true control group, variability in population characteristics, we're comparing this to general population statistics we certainly know that obesity is a risk factor for cardiovascular disease. We know that exercise can be a trigger for myocardial infraction and sudden death. The population statistics don't pick out the population. You also heard this morning that 50 percent of the AERs had other risk factors.

The population-based statistics especially in the younger populations -- I don't think they collected that data but certainly in women under the age 45 I don't think that 50 percent of them have significant risk factors for cardiovascular disease. And, of course, we had to use a range of incidence.

In summary, this is not an attempt to prove or disapproved an association between ephedra and adverse events. However, even under our estimates that

we believe are likely to overestimate incidents of events in ephedrine users, the estimated rates of seizure, strokes, and MIs among these users may be consistent simply with the background rate of events expected in the absence of ephedrine use.

Based on this and the other data that you will hear from our other panel members, I will read our consensus to the first question of the association.

The panel feels that the available information does not demonstrate an association between the use of dietary supplements containing ephedrine alkaloids and serious adverse events when used as directed, and I would define "as directed" according to the AHPA trade recommendation; which is serving limits of not more than 25 milligrams of total ephedrine alkaloids, and total daily consumption of not more than 100 mg of total ephedrine, and appropriate warnings, all we believe consistent with over-the-counter available ephedrine alkaloids products.

The next question are there indications for dietary supplements containing ephedrine alkaloids? The panel didn't have a lot of time to review information on this but I will go through a little bit next slide. These were some multiple dose studies, again, now, over-the-counter ephedrine looking at

weight loss. And the purpose of putting up this slide is two fold. One, to show you that there are studies that have shown weight loss, as you heard about this morning, with ephedra. They are small studies they are limited but the certainly support the hypothesis that this is effective for weight management.

We also were able to review a randomize placebo-controlled study right after Huber -- and he will be presenting this study as I understand, tomorrow, looking at three different dietary supplements containing ephedrine alkaloids, randomized placebo-controlled which showed significant weight loss with all three, and no significant effect on heart rate or blood pressure.

So are there indications? Well, based on a review of these data we believe the dietary supplements containing ephedrine alkaloids may be useful in weight management.

The third question, are outcomes associated with user characteristics? You're going to hear some issues about this from other panel members, but our conclusion is or our consensus is that given the absence of data clearly demonstrating an association between ephedrine dietary supplements and serious adverse events when used as directed, the presence or

absence there was this acceptable population cannot be determined.

However serious overdosing and overuse can lead to serious adverse events, minor and/of very rare idiosyncratic reactions may occur including skin reactions and allergic reactions with use at recommended serving sizes as they came with any ingested food.

The PPA and hemorrhagic stroke study was we were made aware of this after our panel met for their consensus so the panel didn't have a chance to review the study. I reviewed the study from epidemiological perspective. I understand others are going to present this in great detail. I'll give you my own quick conclusions. I don't think that the study was sufficient. I think that were several severe limitations which prevented definitive conclusions about the association between PPA hemorrhagic stroke from the study.

Finally, the other consensus statements reached bt the panel, I'd like to just go through some of those. I think these are important; we thought about this a lot. We believe that all labeling of dietary supplements containing ephedrine alkaloids should contain appropriate directions and warnings for

the public as adopted by AHPA and similar to those approved for over-the-counter ephedrine alkaloids products.

We also believe that these should be readily legible and available to the consumer for prior to purchasing the product.

You'll hear pathology data by Dr. Hutchins but their consensus statement was that the pathology data available do not show a pattern that is consistent with ephedrine alkaloids containing dietary supplements as a cause of death. We believe that an independent multidisciplinary panel should be assembled to perform a clinical pathologic review of all death reported to FDA.

We also believe that in order to provide a more comprehensive scientific database, the National Institutes of Health, The Department of Health and Human Services and industry should work together to consider further controlled studies to address unresolved issues.

Our last slide, we believe that very strongly that preparations that contain ephedrine alkaloids and that are marketed without responsible label instructions, serving size limitations, or are marketed with claims of achieving an altered state of

consciousness or euphoria including so-called street drugs should be prohibited because they promote excessive use and abuse.

And with that I will end and turn it over to Dr. Page.

[Applause.]

DR. PAGE: Thank you, Dr. Kimmel. Could we have the first slide.

Panel, I am Norbert Page, and I am a partner in Toxichemica International.

I'm going to speak very briefly about the published literature on the adverse effects of ephedrine alkaloids containing dietary supplements. To save time I'm going to refer to these really as ephedra products.

I might mention that I am a consultant at this time to the Ephedra Education Council, but as you'll see from this slide I've been allied with doing hazardous assessments and risk assessments with federal agencies for some time. I've been on the staff of a number of the health agencies. The only one I really haven't been on has been the Food and Drug Administration. But I'm consider myself fairly knowledgeable in the area of the hazard assessments and risk assessments prepared quite a large number of

criteria documents for the various agencies.

I'm going to focus specifically on the FDA's literature report. Now we have done an independent review of the published literature and we will be providing some additional references to the FDA docket. But I want to specifically address some of the structure of the FDA report.

First of all, I want to complement Dr. Love and staff. They did a pretty good job of actually searching and retrieving the bulk of the literature. So we've go a few that we're going to add but they have done, I think, an excellent job of getting the literature.

I have some serious problems in the interpretation. My major concern however is that they are relying very heavily on the PPA literature to analyze the health effects of the ephedra products. In my opinion this is not scientifically appropriate.

Why do I say that? First, PPA is present only in very small amounts and it is also only in a few of the ephedra products -- going to go into that. Also there is only a very minute amount of ephedra that is metabolized to PPA.

A third reason, there's substantial pharmacological and toxicological differences between

PPA and both ephedra a pseudoephedrine the main alkaloids in ephedra products. I won't dwell with this third issues since we have other speakers who will.

I'm going to talk now about PPA in ephedra products. I might mention that you already seen one slide I think it was earlier by Dr. Fong and his data pretty similar to what I have here, I think he had 40 to 90 percent ephedra, whereas I came out with 30 to 90 is the generally accepted amount in ephedra products.

But as you can see from here the really two major ephedra alkaloids, ephedrine and pseudoephedrine. There's a few others, the methylephedrine, and PPA in very small amounts and usually not existing.

Let's look a PPA in the commercial ephedra products. There have been a number of studies that have looked at this. I'm going to show the two Dr. Gurley and his team. In the first one in 1997 they looked at six of the ephedra products, three which had no PPA and the other three had very small amounts, and this is percent of the total alkaloid content .61 .3 and 3.1.

Dr. Gurley had another study, the should be down here, but in the study in recent study in the year 2000 he expanded it and actually looked at 20 ephedra products. And he found that in 14 he found no PPA at

all. In the other six there were very small amounts. .16 to .25 milligrams per dose.

Now, keep in mind that I think you've heard that there may be as much as 20, 30 milligrams in a dose, perhaps even more, but that's what we will -- so we we're talking about a very small amount.

Lee also recently published and where he found 3 percent of the total ephedra alkaloids which are used TEA consistent of PPA. Betz in 1995 who used to be with FDA also review that the alkaloids content and he found in his first paper about 5.1 percent but in another study more recently he looked at nine of ephedra products and these are popular products he took off-the-shelf, and of those nine, he did not have PPA and two head trace amounts. .2 percent and 1.8 percent.

So I think you can see from here there's very little in most products there's no PPA. In those products that do have PPA, it's extremely small amounts.

Let's take up the issue of metabolism of major ephedra to PPA. Ephedrine can be demethylated to PPA, however, the amount of demethylation is extremely small. It varies with the publisher. Beckett and Wilkerson found about 4.3 percent metabolism. Bob and et al used both methods and they found 4 percent in 4.3

Basalt and Cravey in '97 came over 4 percent.

Now the FDA has used Dollery's report where they show 8 to 20 percent metabolism. I want to point out that Dollery is a secondary reference and it is actually a 1975 publication that Dollery used and in that there is not much information as to the individual so we really don't know much about whether there was any underlying situation that may have promoted the metabolism. What we do know though is that if an individual has an alkaline urine, this is a study by Wilkinson using Ph of eight, this does increase the metabolism of ephedra to PPA. The fact that their study it went up to 18.2 percent. But, by and large in normal individuals metabolism is rather minimal around 4 to 5 percent.

The other issue is it appropriate to use other routes of exposure. We were talking about ingestion of dietary supplements, is it appropriate to use products that are given by nasal spray or inhalation? And my opinion, I think this is appropriate. The alkaloids in ephedra products according to the references I've listed, they are absorbed slower than at pure alkaloids but the basic pharmacokinetics in the metabolism is quite similar. So I don't ever problem with using information from

other routes.

I want to present one paper that I think is kind of interesting in deals with the pharmacokinetics it's also cardiovascular effects, I won't be talking about the cardiovascular effects since someone else will. But in this study, Wyden, et al, subjected 12 subjects to 25 milligram dose of ma huang twice in one day, in other words he had a total dose or 50 milligrams and they measured the blood pressure and also they sampled the blood quite frequently.

And just to speed up there's no PPA in this product and it is primarily ephedra. And what they did they compared the pharmacokinetics for ma huang capsules which is finely powered herb to that of ephedra tables and ephedra solution.

Here are the results. Basically absorption is nearly complete for all three forms; it's readily absorbed, I don't think there's any debate about that, the elimination Kinetic is pretty straightforward, it's one compartment first-order model and that seems to be consistent across the literature. They did find that there is slower absorption from capsules than from tablets or solutions. The main thing in the capsules is there is a longer period of time to reach the maximum time peak level in the blood. It's getting

close to four hours compared with less than two if it's in the tablet or solution form.

In other words, you've got the absorption coming in a little bit slower, reaching the peak at a later time; whether that is significant or not in valuation I'm not sure. But the half time is basically about the same. Gurley also did a similar study and he found a slightly slower absorption to ephedra alkaloids from pills than from gel caps. So it seems like a pretty good system.

Now, I want to get into the extent of the literature. There's only a few reports that actually deal with the adverse effect of ephedra products. And the FDA has concluded, however, the literature on ephedrine and pseudoephedrine in medical products; for example those used in asthmatic preparations and so on. They also included the literature on PPA medical products.

Real quickly, these are the 11 articles that have been published pertaining to the ephedra products themselves. There's a fair amount of literature on the ephedra -- I mean, the epinephrin, ephedrine and the pseudoephedrine which has also been prepared and available in the FDA's document. But, anyway, there are only 11 journal reports involving 12 cases.

Two serious events, one is a death and that was an athlete with existing cardiac pathology. But the pathology has been there, according to the pathologist, for a couple weeks and it was a necrosis with repair. There had been no exposure to the ephedra products within the prior 24 hours. In addition there were other risk factors which I have mentioned. So, therefore, the association with ephedra product I think is really questionable.

Second major case is a stroke and this was an infarct. The man was engaged in intensive body building and he's consuming excessive amounts of many products in addition to the ephedra products. He also had a congenital heart defect, patent frame in the valley, but it's a clear case of overdosing with many products and there are also the other risk factors.

This is a list of the other papers in the literature on the ephedra products, not as serious, and one thing that does stand out, there were three cases out of the five where there's a previous history of psychiatric conditions, whether the ephedra product had any role or nor in these cases is open to question. It would appear though that temporal relationship a couple of those cases may have been related to dietary product. But there are other risk factors involved.

On the two hypertension cases these were definitely related to overdosing. In fact one of the cases the individual had consumed in one does more than four times the daily allowance as recommended on the label. So it was strictly overdosing.

Hepatitis, one case. It is not clear the role of ephedrine alkaloids, in fact, the author said there's something in the dietary supplement that probably triggered this not necessarily ephedrine, but it could be some other product. One thing it did look like it was immune mediated hepatitis. On intulethias there was long-term, high does use, you see the levels there that's extremely high doses and the individual also had a diet high in protein and calcium, and acolytes, very low fluid intake.

The other thing is, it is certainly related to ephedrine in this case since there was ephedrine and pseudoephedrine measured in the calculi.

The last case is erythroderma. This occurred about eight hours after the individual ingested Chinese herbs. There was a history of prior sensitization and reactions to the over-the-counter alkaloid products ephedrine and pseudoephedrine

In summary it's my opinion that the PPA literature is not relevant to this analysis of ephedra

products the reasons for the reasons I have stated. Also, the few reported serious adverse effects from the injection of ephedra products were related to excessive consumption, the overdose are due to other risk factors. Thank you.

[Applause.]

DR. PAGE: I'd like to introduce Dr. Steven Karch.

DR. KARCH: Good afternoon. My name is Steven Karch. I'm an assistant medical examiner in San Francisco. I'm a cardiac pathologist, my principal interest is in the investigation of drug-related deaths, my textbook on the subject is generally considered to be the standard text and it was quoted extensively in both the 1997 iteration and in the parent literature review.

We're going to speak -- my comments are confined to cardiovascular complications of the ephedra alkaloids.

The AERs will be discussed shortly by Professor Hutchinson. Briefly, he found no consistent pathologic changes or any evidence that the epidemic or ephedra exposure was responsible for any of the deaths reported.

My own review is consistent with his findings

and I've have had the opportunity to examine several of the hearts of from these individuals, and my own review is that there is no consistency of clinical or pathological pathologic features apparent.

Part C of the FDA docket is entitled review of published literature on toxic effects of ephedrine alkaloids and it deals mainly with purported cardiovascular and neurologic complications. It contains 94 references of which 38 or 40 percent refer not at all to the primary literature, but only to meetings and textbooks.

Of the 56 citations to the primary research literature almost all are the case reports none are the prospective studies; 12 of these were to pseudoephedrine amounting to 21 percent; 19 or 34 percent just about a third related to ephedrine and more than half, 24, were about phenylpropanolamine. It is clear from reading this document that the FDA considers all isomers of ephedrine to be equivalent both in terms of effects exerted and toxicity produced.

This clearly is not the case and there are new fairly recent in vitro studies demonstrating, for example, that a naturally occurring 1R2S isomer has much greater affinity for beta one and beta two receptors than does synthetic pseudoephedrine and that

conversely phenylpropanolamine has much less affinity. In spite of all these very clear differences at the molecular level the FDA relies so heavily on the phenylpropanolamine data to raise questions about the safety of ephedra and I feel that is inappropriate.

In addition the FDA literature review contains a number of what I feel are simply misleading and/or simply mistaken conclusions.

For example, the FDA says vasculitis with ephedrine is particularly likely when used in combination with the phenylpropanolamine or caffeine. However, the two citations offered in support are about cases where ephedra or ephedrine was not even ingested.

The FDA says ephedra and phenylpropanolamine are listed as commonly abused, stimulant drugs, and the source if you track it down, is a 1994 textbook which in itself contains no reference for the statement. At the same time the FDA has chosen to ignore the paucity of mentions in other documents like the household survey and so forth.

The FDA literature review includes data which contradict some of its own conclusions. The FDA says a significant increase in diastolic and systolic pressures occur in normal intensive subjects with oral doses of ephedrine equal to or greater than 60

milligrams. The sole support for this statement is citation 82. This statement is a paper, it's a review paper and it discusses seven earlier studies that were done normal tensive individuals; half of whom showed no change whatsoever in blood pressure

At the same time the FDA fails to mention a series of studies done by exercise physiologists which have demonstrated no blood pressure effect even with maximal exercise stress testing.

I've listed some of these here for you, and you'll notice that not all of them are new, so I'm not sure why they weren't picked up and included. For instance, Bright in 1981, gave 120 milligrams of pseudoephedrine to six healthy males and subjected them to submaximal stress testing. There was no change in recovery time, there was no change in systolic pressure, there is no change in diastolic pressure, and there was no change in heart rate maximal heart rate or VO2mas.

Clemens in 1993 did placebo trials these were double-blind, double dummy. Ten healthy women exercising maximal exercise and I truly mean maximal. These are VO2maxes of up to 60, treated with pseudoephedrine, had no changes a recovery time, maximal pulse rate, diastolic or systolic blood

pressure.

In Dr. White's study published in 1997, variable effects were noticed in 12 volunteers given 20 milligrams of ephedrine, but in the half that did experience an increase in blood pressure, the increase was confined to 8 millimeters. And I'm hard-pressed to believe that eight millimeter increase in systolic pressure not in diastolic was at all significant

And, finally, and more recently is the paper by Rosanne in 1999 120 milligrams of pseudoephedrine every 12 hours to a group of, I think it was a dozen volunteers, healthy males. In a simulated weightlessness, again, had zero affect on any measurable cardiovascular parameter.

At the same time that these studies have been ignored through important papers on the effects of measured exercise that have not been mentioned either and I think their mission is wrong. Some of these are very convincing studies such as the paper by Bell and Jacob which appeared in Aviation and Space Medicine last year, the study involved nine healthy male, recreational runners, these were not professional athletes, they were just fit people who did what is called the Canadian Forces Warrior Test, which is something that's a part of the Canadian Army basic

training. And these people ran a 3.2 kilometer course wearing about 25 pounds of combat gear, they ran it with placebo, and they ran it after having taken 375 milligrams of caffeine and 75 milligrams of ephedrine. There was no change in systolic pressure there is no change diastolic blood pressure, there was no change in maximal pulse achieved, there was no change in recovery time, the only change achieved was they exercised longer.

I find this particularly difficult to accept since I have an interesting cardiomyopathy. The FDA says cardiomyopathy has been reported with use of ephedrine, and I think I might have cited as one of the sources. In fact there only four cases in the world literature alleging a ephedrine cardiomyopathy. And you will note that the first was a 35-year-old man taking 400 milligrams of ephedrine per day and liberal doses of prednisone for 14 years.

The second person was a 28-year-old 321-pound, cigarette-smoking-woman who was taking two grams 2000 milligrams of ephedrine per day for eight years.

And the third was another woman, I believe she was also overweight taking more than 1000 milligrams a day for ten years.

The only other case, and I wouldn't have

cited it, bit it is cited in the FDA document, refers to 14-year-old who developed heart failure after taking 225 milligrams of phenylpropanolamine in a suicide attempt.

The FDA says that myocardia ischemia and infarction have been reported. Well, yes, that's true but seven of the eight citations offered are cases that involve phenylpropanolamine. And the one case involving an ephedrine user was an ephedrine nose drop abuser who was taking ephedrine, six milligrams an hour, every hour, every day, for many months.

Ephedrine and coronary spasms. Well, again the FDA says cardiac damage may result from coronary artery spasms induced by stimulation of adrenergic receptors. This is clearly true; however, the two citations offered in support both involve patients who been given high spinal anesthetics. One of them was a former cocaine user and probably was a norepeneprine depleted, but be that as it may. They were given high spinal anesthetics which means the heart was deprived of its sympathetic enervation leaving the parasympathetic unopposed, leaving the Alpha effects of ephedrine to be magnified. There have been no other reports of coronary spasms in ephedrine users besides these two.

The relevance of this observation in anesthesiologists is quite apparent, but the relevance to consumers of food supplements is not.

The FDA says shifting of potassium to skeletal muscle following use adrenergic agents like a ephedrine alkaloids may predispose certain individuals to cardiac dysrhythmias. Three references are cited. The first was an attempted suicide who took an unknown amount of pseudoephedrine, theophylline, and no toxicology was performed.

The second referenced citation involves an attempted suicide who took 375 milligrams of ephedrine, 3000 milligrams of caffeine, that would be roughly 50 cans of caffeinated soft drink, and 750 milligrams of phenylpropanolamine. Why the potassium shift should be attributed to a ephedrine in this instance escapes me.

Lastly it was another attempted suicide who took an unknown amount of drug, and no toxicology testing was performed.

Ephedrine and brain hemorrhage. The FDA says a ephedrine and pseudoephedrine have been implicated in cerebrovascular accidents secondary to intercranial hemorrhage and vasculitis. Well, only half of the events that were reported actually involved ephedrine. Most of those were overdoses that occurred in IV drug

users and the diagnoses of vasculitis was histologically proved in only two, and one was taking phenylpropanolamine, the other a combination of ephedrine, caffeine and theophylline. One of the FDA citations No. 71 is actually a letter disputing the diagnoses of cellulitis made in reference No. 64.

When it comes to the comments of the reviewers I feel they have not been as forthcoming as they might have been, and they may have overlooked some things that are important to considering the safety of these compounds. One of the FDA consultants goes even farther than the FDA and -- which considers all the isomers to be identical and considers all sympathomimetic drugs to be the same, there is no other reason to explain the statement that ephedrine shortens the refractory period and facilitates the development of re-entry cardiac arrhythmias.

There have been no published studies of the effects of ephedrine on the electrophysiology of the heart. So I don't really see how the statement could have been included.

Two of the FDA consultants believe that unpredictable variations in individual sensitivity may have caused reactions. One even argues that "we do not know which specific enzymes in the bowel and liver

metabolize ephedrine. Are there individuals who have exaggerated sensitivity to ephedrine products before because they lack a specific P450 enzyme? Well, I have two comments to that. The first is we already know that ephedrine is not metabolized, so I don't see how genetic variation could fail to not metabolize it.

And this morning we were told that the pharmacology of ephedrine was thoroughly well understood. Finally when it comes to individual risk factors, variations of metabolism is unlikely for reasons already indicated. I think individual susceptibility may however be possible due to the presence of undiagnosed medical disorders such as coronary artery disease or even hypertension.

The same considerations of course would apply to caffeine and numerous over-the-counter drugs, and in fact FDA's own consultants states that quote "millions of people use products containing ephedrine, but the number of adverse reactions reported in the United States is now in the hundreds."

In conclusion I believe that ephedrine recommended doses has not been shown to be cardiotoxic but in extremely excessive doses it is cardiotoxic and there's every reason to suppose it would.

Ephedra and its isomer exhibit such different

behavior as to make comparisons among ephedrine, pseudoephedrine, and phenylpropanolamine irrelevant.

And, finally, patients with severe undiagnosed coronary artery disease taking recommended doses of ephedrine may be at risk, but they may also be ar risk from other very widely marketed products.

Thank you for your time.

[Applause.]

DR. FARBER: Good afternoon and thank you, Dr. Jones, and panel members for allowing me to address you. I am Theodore Farber and I have a slide up here that just gives you something of my relevant background Ph.D. in pharmacology in 1960; 40 years of experience as a toxicologist; board certified as a toxicologist in first class of board certification. I have been recertified four times over the last 20 years.

I am a principal in toxic chemica International. Dr. Page is my partner and close associate.

I serve almost 24 years in federal government. The last four years of my service was as director of the Health Effects division in EPA's pesticide program. Basically I was the chief health scientists and chief toxicologist for a staff of 120 regulatory toxicologists, probably the largest group of

regulatory toxicologist in the world, and was a member of the senior executives service.

I had the pleasure of serving 19 years with Food and Drug Administration in many diverse positions, the last of which was as director of the Drug and Environmental Toxicology Division, Center for Veterinarian Medicine responsible for the approval of all drugs given to food producing animals here in America.

Can we have the next slide please?

I would just like to discuss -- mention and give you an overview of the 276 adverse affect reports that were released in March if this year.

The normal basis or process for making a hazard evaluation or a risk assessment is a process that takes into consideration human epidemiology data, animal bioassay studies, mechanistic studies and pharmacokinetic data.

You've already heard from Dr. Page and Dr. Karch something about the problems that they have found in terms of the literature support used by the FDA. I'd like to just discuss some of the aspects of the reliability of the advance adverse affect reports.

I and my colleague, Dr. Page, have recently evaluated 276 of these reports on products containing

ma huang which has been assembled by Food and Drug. These reports are completely unfiltered and are largely made up of anecdotic accounts of adverse effects reported by a lay public

Many of the AERs are reported into the system by secondhand parties. Let me state directly right now that these AERs contain and are inadequate database for the purpose of causal analysis.

And that Food and Drug, by using this deficient database has violated its own caveats in regards to the use of AERs for causality analysis.

It's a busy slide and it represents quite a lot. All of the AER files that we have looked at many of them have contained errors, omissions, inaccuracies, inconsistencies regarding the age and sex of the affected parties, the identity of the product, the identity of the ingredients in the product, the dose taken, dose frequency, and dose duration, as well as the adverse effects mentioned in the files.

Some medical records were difficult to read because of the poor handwriting connected with medical records and/or the poor reproduction of those medical records. By combining the total number of AERs lacking medical records with the number of AERs containing medical records, but lacking information on

dose amount, dose frequency, and does duration we found at a bottom line of this file to slide that there were 202 AERs, approximately 73 percent of the file that were missing information for at least one data parameter considered to be essential for any legitimate causality analysis.

This was not a good database and is simply not scientifically appropriate to perform a causality analysis on this database, and to make any regulatory decisions based on such an inadequate database.

These 276 slides really are very, very similar to the files, the AERs that were issued in the original proposed rule period back in 1997. So they are not really any significant improvement over what we have seen before.

I said FDA has violated its own caveats. In portions of the proposed rule docket there were innumerable places in the docket where these caveats were mention as official policy so to say of the agency and I've underlined the last two items. These caveats mention that the accumulated case reports cannot be used to calculate incidents or estimates of product risk. And occurrence or incidence rates cannot be derived from AERs only reporting rates. In using these AERs for causal analysis FDA has once again totally

ignored its own disclaimers inserted into the index files of the AERs regarding inappropriate use of the database for causality analysis.

Very similar caveats can also be found in the current FDA AER web site.

In spite of the misgivings that Dr. Page and I had in regards to the performance of the causal analysis on this kind of information we did perform our own analysis nonetheless. I'm sure that you're not surprised, some of you, at least, are not surprised that our results were significantly different than the results of the FDA.

I've put this slide up to show you another surprising piece of information that we picked up from the reports connected with the most recent release of AERs. What is surprising is that there was a significant lack of concordance between FDA's causality analysis and the causality analysis performed by its outside experts who have expressed their concern about the safety of ephedra products this morning. This slide demonstrates the lack of concordance for some selected but representative AERs.

An excessive and unacceptable level or degree of judgment and speculation is required for the use of these AERs for any causality analysis. It is obvious

that not only from the considerable disagreement between Toxichemicer, our firm, and FDA and the causal causality rating, but also by the considerable disagreement between FDA and its own selected outside reviewers.

There is a significant considerable lack of concordance with the causality ranking for AERs analyzed by Food and Drug and its outside experts. There was lack of concordance between FDA's opinion and its outside experts of 45 percent for AERs that Food and Drug rated as attributable. For the AERs rated by Food and Drug as supportive, there was a 66 percent lack of concordance.

In addition to good case reports a denominator of that is obtained from the treated group is needed for an additional further evaluation on the causality of these reports. We have a situation here where the agency has provided only enumerator of questionable significance and reliability, has not made any effort to determine what the denominator is in the treated group, neither has the Agency made any effort to determine what the nominator and the denominator is in the untreated group, has gone through a similar exercise as that performed and mention by Dr. Kimmel this afternoon.

Further, it's interesting to note that when aspertane was first approved by Food and Drug many years ago, over 5,000 AERs were reported into the agency. FDA stated that the AER system was unreliable and took no action against aspartame.

Indeed the AERs compiled by FDA do not support any causal connection between consumption of ephedra products and other serious illnesses or injuries. Even assuming these reports were all accurate and they are clearly not, there are only approximately 1,200 reports in this file compared to a conservative estimate of consumption levels equal to many billions of servings of ephedra products since 1994.

In particular there's little evidence in this AER file that alleged deaths, strokes, heart attacks, psychotic episodes, and other serious adverse effects occur more often in individuals who conceive ephedra products than those who do not. Further, any of serious adverse effects seen in the entire AER file are more likely the result of pre-existing medical conditions, drug abuse, excessive exercise, or concomitant use of medications and other substances whose use was recommended against on the product labeling.

Finally it is interesting to note that in an internal FDA memo from staffers in Dr. Betz's unit at Food and Drug, these staffers have concluded quote, "that it is possible that the reported serious adverse effects in all of the AERs are reflective of the coincidental background of spontaneous occurrence in the population and are not causally related to the use ephedra products."

In conclusion the use of AERs to determine causality requires considerable judgmental evaluation. The majority -- the great majority of AERs lack a level of detail and are missing key data that are needed for an adequate scientific evaluation. Even experts in hazard evaluation and risk assessment cannot agree on causality due to the unreliable and incomplete data in these AERs. FDA should heed its own expressed concern with the unwarranted use of AERs for causality analysis. And lastly the AERs related to ephedrine alkaloid-containing dietary supplements, if anything, support the conclusion that they are safe; that is, there is no unreasonable risk when they are used according to label instructions.

Thank you very much.

[Applause.]

DR. HUTCHINS: My name is Grover Hutchins,

I'm an anatomic pathologist and as you can see from the slide I got my a medical degree in 1961, did training in anatomic pathology at the John Hopkins Hospital. I have been on the staff of that institution for over 30 years and I'm currently a professor of pathology on the active staff at Hopkins.

My activities are primarily related to the autopsy service and I do service teaching and research work in particularly heart, lung, pediatric diseases mainly based on the autopsy pathology.

I am certified in anatomic pathology and also in pediatric pathology.

I have been asked to review 22 adverse event reports where a death had occurred thought to be in association with the consumption of ephedrine alkaloids. For each case I examined the record for the likely cause of death and attempted to correlate the clinical and pathologic information available in the AER to determine the most probable cause of death.

The determination of causes of death is a routine component of autopsy practice in our institution and I applied the same reproach here using the various levels of information that were available in the various cases.

For the group as a whole I sought for likely

consistent pathologies that could account for the death and with particularly looking for some likelihood that there was any causal role for ephedrine alkaloids in the outcome. As you'll see from the results that I'll present here, I do not find such consistency in this information.

The available information in these reports were really quite variable. Six of those that I reviewed consisted of only of one or two pages of information. One report was quite thorough, 230 pages. The remainder were of some intermediate length. Among the 22 deaths, ten were in women, 12 were in man; the average age 35 years with a range from five days to 59 years, most were in the third, fourth, and fifth decades of life. Thirteen of the cases had an autopsy done. This was not the case in seven and the information was inadequate in two to determine whether or not the autopsy had been performed.

The exposure to ephedrine alkaloids was well documented in 12 of the cases; that is, and I'm referring here to exposure sometime in close proximity to the death of a patient. This information was uncertain the in ten of the cases.

Toxicology specifically for ephedrine alkaloids was positive in four of the cases, negative

in ten, and not done in eight.

The cases divided up into some general categories, and I'll show a series of slides which illustrate these. The first are four deaths that were to me explained by congenital cardiac problems. The first three of these were individuals who had suffered a sudden collapse and were found at autopsy to have an underlying problem which was perfectly capable of having caused their demise.

These involved a disorder of the myocardium, asymmetrical hypertrophy a malformation of the coronary arteries, an abnormal origin of the left coronary artery and an abnormality of the mitral valve.

The fourth case that I included on this list was signed out on the report as simply been congenital cardiomyopathy. I do not know the basis for that interpretation. I do not know if an autopsy was performed, but I have included here in any case since that was the extent of information. Three of the deaths were explain by coronary disease.

In two of these patients, the first and third here, an autopsy was done demonstrated significant coronary artery arthrosclerosis obstructing the vessels. The second patient had symptoms in risk factors which were totally consistent with coronary

artery disease, however, an autopsy was not performed. Each of these patients had taken the ephedrine alkaloids for a varying periods, but in my view the deaths here were explained adequately by the presence of symptoms and findings of coronary artery disease.

In two instances autopsy demonstrated the presence of myocarditis in the heart. This is an inflammatory reaction in the myocardium usually of unknown cause. The one case had taken materials for about a month and other case for one day and did have a positive toxicity, however, since myocarditis is a very well-recognized caused of sudden unexpected deaths, it seems more appropriate to attribute the outcome to that.

Four of the cases were explained by cerebral vascular disease. None of these individuals had an autopsy performed. The information on exposure was very unclear. Two of them, the ones at the bottom were the 12 most probably hypertensive hemorrhages in the context of pre-existing hemorrhage. One, the second an intercranial aneurysm and the first a carotid occlusion of unknown cause.

Two of the deaths were explained by aortic dissections. This is a tearing of the wall of the aorta, typically occurs in the context of some

abnormality in the structure of the aortic wall and is in many instances has a familial basis.

The fact that in the first case the aorta was found to be dilated and the second case there was a very strong family history of aortic dissection. It seems far more probable that this is that genetic form of weakening of the connective tissues of the aorta that predisposes to dissection.

These were both discovered at autopsy, however, exposure to ephedrine alkaloids was unclear in those cases. There were to me a interesting group of cases, unfortunate outcomes of individuals who were doing very strenuous fasting and exercise and exposure to high temperatures in the first two cases listed their the death in the first case was related to a hypothermia to 108 degrees, which is really phenomenally high. He had not been exposed to the agents for at least two months prior to his death.

The other two cases the deaths were due to radnomyalysis which is a breakdown of muscle in the context of extreme exercise. Again, there was one indication of bile that was positive for the agent. Blood was negative, and in the other case there had been historical information of exposure, but no toxicology was done.

There are two sort of odd deaths, if you will, in a sense a five-day old premature child died of necrotizing enterocolitis, this is an entity of uncertain cause associative with prematurity and with the early feeding. It probably has at least in part and infectious etiology. The exposure here was related to maternal intake of ephedrine alkaloids and the connection to my view is kind of unclear.

The other case the clinical information was scant. I have characterized as with the flu-like illness because there were pulmonary symptoms. The individual also had symptoms that could have been related to cardiac problems that had been going on for some days. She had stopped exposure a week before the death and no autopsy was performed.

The final category are two explained deaths despite careful autopsy it was not possible to arrive at a conclusion as to what the cause of death was in these individuals. Both have had exposure to the agents and these, in my view, remain in that category of unexplained outcomes.

In summary among the 22 AERs that I reviewed, explanations for death were found in 20 of the cases; these were all well-recognized causes of death in the general population albeit some are rather uncommon

others common. In the two cases where the cause of death was unexplained and this is an incidence that is consistent with general experience with autopsies if you really look at your information critically you really don't understand in some cases why the individual has died.

In conclusion I found no consistency of clinical or pathologic features in the group of cases, nor was there evidence to show that exposure to ephedrine alkaloids was a contributing or causative factor in the death from my perspective.

It is only in the two unexplained deaths the use of ephedrine alkaloids could be a speculative explanation for that outcome.

Thank you.

[Applause.]

DR. HUTCHINS: Dr. John Olney will now speak.

DR. OLNEY: I'm John Olney, Professor of Psychiatry and Neuropathology at Washington University in St. Louis. I have 30 years' clinical experience as director of the psychiatry consultation service at Washington University and a thirty-year research program in the neuroscience funded by five different divisions of NIH as are listed there

For research focusing on stroke, perinatal

brain damage, epilepsy, head trauma, Alzheimer's disease, schizophrenia, drug addiction, and fetal alcohol syndrome.

I have also conducted food toxicology research. Thirty years ago I discovered that monosodium glutamate, MSG, a widely used flavor additive destroys nerve cells in the immature hyperthalmus or brain.

Twenty years ago I discovered that the artificial sweetener NutraSweet also has the same neurotoxic properties. And I have also published evidence potentially linking NutraSweet ingestion to an increased incidence of malignant brain tumors.

I've received several awards, one of them listed there from NIMH, that's the National Institutes of Mental Health. That was to perform research as a career scientist. That award has been renewed every five years for the last 30 years. And I've received other honorary awards and elected member to the National Academy of Sciences.

Why am I here? I'm serving as a consultant to the Ephedra Education Council. Specifically they ask me to evaluate evidence pertaining to the potential of ephedrine alkaloids to cause or contribute to neurological or psychiatric disorders.

The evidence I've examined includes the adverse event reports putatively linking ephedrine alkaloids to nervous systems disturbances including all of the adverse event reports review for FDA by outside consultants.

Drs. Ricaurte and Stoll from also have examined the world literature pertaining to the effects of ephedrine alkaloids on the nervous system of humans or experimental animals.

Concerning the adverse event reports, FDA identified 28 adverse event reports pertaining to the nervous system. However, FDA disqualified 12 of these reports because they provided insufficient information. Nevertheless FDA submitted all 28 reports to two outside consultants, Drs. Ricaurte and Stoll and asked them to rate each report in terms of how strongly it links of ephedrine alkaloids to an adverse event.

Doctors Ricaurte and Stoll found only two cases that they agreed were strongly linked to ephedrine alkaloid ingestion. Remarkably both of these cases were among those that FDA had already disqualified due to insufficient information. This signifies that FDA and their two expert consultants have not identified a single adverse event report that they can agree closely links ephedrine alkaloids to

adverse nervous system effects.

In a cover letter to FDA, Dr. Ricaurte stated that ephedrine alkaloids pose a health risk. But the risk he identified pertains not to the general public, but to specific individuals who have a predisposition to certain illnesses or who ingest ephedrine alkaloids and/or other stimulants in abusive doses. This places ephedrine alkaloids in the same category as sodium chloride, or common table salt, which poses a health risk not to the general public but to individuals who are predisposed to high blood pressure or certain kidney and heart diseases.

There are many such food-related substances that FDA considers so harmless for the general public that they require and are given no regulatory attention.

Concerning the world literature, the most reliable evidence comes from randomized, placebo-controlled, human trials that demonstrate that the industry recommended dosage of ephedrine is 25 milligrams taken not to exceed four times per day is not associated with a significantly higher incidence of adverse nervous system effects compared to placebo-controlled.

Concerning animal studies, they do not

demonstrate a neurotoxic action of ephedrine unless administered at doses that would be considered massively abusive in a human context.

If one wishes to discuss the studies by Dr. Ricaurte that he referred to in squirrel monkeys we could perhaps discuss the doses used in that study later on.

Concerning the FDA position, it is not clear to me what position FDA espouses, but FDA appears to believe that dietary supplements containing ephedrine alkaloids are hazardous to the public health.

I will share with you my observations regarding this apparent FDA position. It appears that the FDA position is self-contradictory. For many years ephedrine and its analogs have been marketed as over-the-counter drugs -- several decades, and FDA has shown no concern about the adverse effect potential or abuse potential of these agents even when consumed together with various sources of caffeine and large amounts of caffeine from coffee, tea, caffeinated soft drinks, and so forth.

The logical conclusion arguing from this FDA precedent is that FDA does not really believe that ephedrine either alone or in combination with caffeine poses a public health hazard. If they did believe that

they would have already been trying to develop more stringent regulatory control for the use of over-the-counter ephedrine drugs together with these various sources and heavy intake of caffeine.

The FDA position does not seem to be substantiated by evidence. If FDA believes that ephedrine alkaloids when consumed in reasonable doses in reasonable doses or hazardous for the nervous system; this belief is not supported by a single adverse event report. FDA and two expert consultants could not identify any adverse event report pertaining to the nervous system that they could agree was strongly linked to ephedrine alkaloid consumption. So that FDA position is not supported by a single adverse event report. It's not supported by the world literature and it's not supported by the FDA precedent. In fact it contradicts FDA precedent.

Now, I want to say a word about health protection standards. First I will discuss AHPA standards AHPA being the American Herbal Products Association. AHPA has developed a sound health protection standards -- set of health protection standards including responsible label practices which is enforces upon its membership.

For example, AHPA sets doses limitations for

ephedra products not to exceed 25 milligrams of ephedrine per serving, four servings per day, and AHPA recommends that individuals with high blood pressure, heart disease, or various other illnesses consult with their physician before using a ephedra products. These are sound recommendations simply because its best to err on the side of cautiousness and on the side of consumer protection.

I want to compare AHPA and FDA standards using a couple of examples. Table salt is hazardous for individuals with high blood pressure, but FDA allows table salt to be sold in bulk or added to processed foods without warning labels. Ephedra products if used in doses recommended by AHPA, appear to have little or no effect on blood pressure. Nevertheless, AHPA warns individuals with high blood pressure to consult their physician before using ephedra products.

Caffeine, a known stimulant, is present in high concentrations in many products: coffee, tea, caffeinated soft drinks, and so forth, and is ingested chronically, in large amounts, by millions, tens of millions of consumers, some of whom are in this room. There's no proof that ephedrine alkaloids are less safe than caffeine, but AHPA recommends that ephedra

products be used in restricted doses, whereas, FDA does not attempt to restrict the public consumption of coffee, tea, or caffeinated soft drinks.

These are very simple examples that I've used to set the stage for making the point that AHPA seems to be taking a responsible approach. So that you fully understand where I'm coming from, let me mention that over the years I've been critical of FDA for their failure to require adequate warning labels on foods that contain additives that have potentially toxic side effects.

It has not been table salt and caffeine that have been the subject of my concern. It is substances like monosodium glutamate substances that are toxic to the immature brain, and these are substances that FDA allows to be added to foods in any amounts and fed to infants and children without any warning labels at all. It is my belief that food products should be regulated very carefully, and I don't care personally whether the regulation is done by FDA or by the industry itself. But I do want to the regulations to be responsible from a consumer protection standpoint, and to be effective.

Let me close by saying that based on all of the evidence that I have examined and based on standards that are more strict than FDA ordinarily

requires, I consider it reasonably reasonable to conclude that ephedrine alkaloids contained in dietary supplements are safe if used in doses recommended by AHPA and if used in keeping with all other APHA-recommended label instructions. And I might add that if FDA and APHA or other similar organizations could get together and draft some regulations similar to the guidelines already being followed by AHPA it seems to me that that would be a gigantic step forward.

Thank you.

[Applause.]

MR. ADAMS: Good afternoon. My name is Edgar Adams. I'm a senior vice president at Harris Interactive and I was asked to review some of the data on the abuse liability of ephedra -- products containing ephedrine alkaloids because in several of the reports by FDA and their outside consultants references have been made to abuse liability and addiction. And in one of the reports a typical addiction case is actually referenced.

I am currently senior vice president for clinical research at Harris Interactive. Many of you have probably not heard of us, we conduct the Harris Poll which you probably have heard of.

I'm a principal investigator, I study

investigated abuse liability of tramadol verses -- and hydrocodone in over 11,000 subjects. And also current principal investigator on a study looking at the abuse liability of nicotine replacement therapies in over 1,300 subjects.

Previously I spent 23 years actually 23 years five months in the United States Public Health Service and was director of the division of epidemiology and prevention research at the National Institute on Drug Abuse.

There, among other things, I was responsible for the drug abuse warning network which is a measure of consequences and not prevalence associated with various medications and other drugs of abuse such heroine, methamphetamine, et cetera.

I was also responsible for the household survey and served as an advisor to the Pompidou Group of the Council Europe as a expert in drug abuse epidemiology.

As you can see, my educational background is pharmacy, pharmacology, and I have a degree in health policy evaluation and management.

I reviewed cases that were possibly associated to what abuse independence and misuse including the two cases that were included in the

insufficient data group because of intentional misuse or abuse. And to the extent possible I compared the information in the reports to the diagnostic and statistical manual of the American Psychiatric Association for abuse and dependence. I also looked at the data from the drug abuse warning network from 1989 through 1998.

Now, before I show the data let me review some definition, and these are definitions of part the harmonization between the World Health Organization and tbe diagnostic and statistical manual.

Misuse is usually identified as repeated use of a drug for nontherapeutic purposes. An obvious example is the use of a nicotine replacement therapy to avoid smoking regulations such as smoking on a plane.

Abuse or the WHO classification, harmful use refers to repeated misuse that causes damage to health or problems in social, occupational activities, or other legal obligations. The key here is the there is repeated use and there is an impact on obligations or developments of other problems.

Dependence. In both ICD10 and the DSM4 Manual focuses on the loss of control over the use of a drug including consequences. While it includes tolerance and dependence neither is necessary or

sufficient.

Withdrawal refers to a time-limited syndrome that occurs in concentrations of use and which symptoms that are clinically or functionally significant. Everybody recognizes that heroin causes withdrawal but so do many other drugs including steroids tricyclic antidepressants.

The DSM4 criteria for substance abuse basically is one of these four criteria, and, again, as I outlined -- I'm not going to go through each one -- but you can see they all require recurrent substance abuse and either failure to make obligations which are used in situations which are haphazard, legal problems such as being arrested for substance-related or disorderly conduct, or driving while intoxicated, and continued substance abuse despite having persistent or recurrent social or interpersonal problems such as fights with spouse.

B says you cannot be an abuse if you've ever been diagnosed for dependence for this class of substance. The criteria for substance dependence require three of the following: no tolerance or withdrawal are there, basically taking larger amounts to get the same effect, withdrawal, the substance taken in larger amounts over a longer period of time that was

intended, a persistent desire or unsuccessful efforts to cut down or control substance use, a great deal of time spent in activities necessary to obtain the substance, uses substance or recover from its effects, important social occupational or recreational activities given up or reduced because of substance use, and use despite continued knowledge of having persistent or recurring physical problems, such as an ulcer made worse by drinking.

I am not going to try to discuss this slide. I realize it is busy. All I wanted to show is two things. One, I looked at the products that were being taken; age, sex, weight, reason for use, the dose that was taken, the duration, of use, the content, whether it had ma huang, ephedrine, caffeine, et cetera; whether or not the person was hospitalized; what the adverse events that were described were and what the outcome was.

You can see a lot of missing data up there. I picked one case. This is case 11918 which is actually the case that is cited in one of the expert reports as being a typical case of addiction. If I didn't note it, let me note it now, while we often refer to as drug addiction, in the clinical sense there's no such thing as addiction.

You will note that the WHO and DSM criteria did not have the word "addiction." It's usually dependence. And when people think of addiction they typically think of compulsive use. But the appropriate clinical term is "dependence."

The product used in his case was Be Thin Again. It was a 38-year-old female taking the product for weight loss. She wanted to lose weight for wedding. When she bought the product she was told the five tablets a day which was the maximum recommended dose would be safe. It was suggested that she take three tablets per day, which she did, then later on she began to lose weight less slowly -- or less rapidly, I'm sorry, and went up to five tablets per day again on recommendation. That recommendation, by the way, it's unclear where it came from. I'm assuming it came from where she bought the product

She took the product for 19 months it did contain ma huang, she was not hospitalized, she did experience mood changes, became argumentative, and abusive. When she recognizes it happening, she stops taking the medication; there's no indication in her own letter whether or not she had problems too stop taking this. She did state that she felt addicted to the drug and that's why she stopped taking it.

Again, these are the cases. I am not going to go through them all. However, it would appear that by the criteria listed in the DSM4 that this woman, which is the third case here, was in fact abusing the drug. She did take it after she began having fights with her husband and abusive arguments, et cetera. So it would appear that she was abusing drugs. She was taking it for a longtime and was experiencing some of the side effects associated with long-term use of sympathomimetic.

Case 12837 technically is not an abuser. He said that he began using the medication and resumed cocaine use. So he became a cocaine dependent, and based on criteria he would not be considered an abuser here,

The first two cases which I won't discuss other than to note that that all the no -- are the two cases that were thrown out by FDA as abuse or misuse. Essentially they were overdoses, one of which was an intentional overdose.

The next thing I want to talk about is Dawn. Essentially Dawn was set up to look at the consequences associated with drug abuse, to monitor pattern of trends of new abuse entities. For example, in the 80s tees and blues followed using the Dawn system. In Dawn

drug abuse is defined as the use of prescription drugs in a manner inconsistent with acceptable medical practice; the use of over-the-counter drugs contrary to approve labeling. In other words if it says take an aspirin twice, four times a day, and you take three aspirin or four aspirin then that technically meets the criteria for abuse in Dawn. And the use any of other substance, heroin, cocaine, marijuana typically abuse drugs for psychic effect, dependence, or suicide

And these are the third piece there of what really Dawn is most useful for, for a variety of reasons. There is one other comment. Suicide the intentional overdose is not a symptom of drug abuse. It is not part of any other diagnostic criteria and should be excluded from Dawn data anytime that you look at the data for abuse concerns.

Other psychic effects which is part of another definition is use of a drug to improve or enhance any mental emotional or physical state, and these are actually reduced pain, stay awake, relax, help study, et cetera, from the Dawn report.

Three points here. One is, you can see that's there was an increase -- these are ephedrine episodes in Dawn, 1989 to 1998. You can see that there was an increase in the mid-90s and then a decrease in

the last two years, basically roughly by 50 percent.

You can see that in terms of all the evidence of Dawn these average around 0.2 percent; clearly less than 0.5 cents percent of all mentions, usually about a third are in combination with alcohol which could account for some problems.

Essentially the Dawn data are now projected to estimate the number of cases that might occur in all the hospitals in the United States that have emergency rooms, which is between three or 4,000 with all the consolidations it's hard to know; but essentially you can see if you look at 1989 that the weighting factor for drugs like ephedrine and other typical over-the-counter products is somewhere between 8 and 10. So that 1,119 is based on about 120 to 150 reports in the hospitals that report to Dawn. The key is that despite the increase in use of the products, the consequences associated with use, at least measured by the drug abuse warning network, seemed to be decreasing.

To reiterate, the number of mentions of ephedrine in Dawn have decreased substantially, by 50 percent in last two years. Reported ephedrine Dawn cases are likely to have been attempted suicide, in fact, more than half are attempted suicide. And in comparison, other over-the-counter medications the same

indication. You can see that acetaminophen accounts 32,000 episodes, ibuprofen 17,000, et cetera.

So, in conclusion on this piece the Dawn data suggested a decline in consequences associated with ephedrine. The majority of the consequences associated with suicide attempts which were inappropriate in looking at abuse.

Finally, it would appear that based on the adverse events there is not a significant -- I see the red light going off, this is last slide.

There's not a significant evidence of widespread abuse of the product. And in fact a meeting held on the sole issue of abuse in 1999, reached essentially the same conclusion, and that was basically backed by the federal government's nonsupport of international scheduling and these consequences are reenforced by the millions Americans that use these products apparently without consequence.

If there were significant problems you would expect to see the Dawn data and other indicators increasing substantially.

Thank you.

[Applause.]

DR. JONES: Thank you Dr. Adams, and to the panel, again, for respecting time and keeping things

concise and to the point.

Let me turn to my colleagues for questions, Dr. Salive.

DR. SALIVE: Marcel Salive, NIH.

I have a question. You reviewed all the case reports and I understood the comment about possible role of coincidental effects in these cases and I wanted to ask about positive rechallenge, whether any -- there are some cases cited in the FDA report where the adverse event occurs with the use the product, the product is stopped and then product is readminister and the same sort of symptoms reoccur. I won't ask the pathologists about this, only the clinicians but were their cases of that? I believe there were some dermatologic and possibly cardiology.

DR. FARBER: What you're talking about is a fundamental set down by Coke many, many decades ago, and, yes, there were some cases but very, very few.

DR. KIMMEL: I'm sure we have the number somewhere I do not think anyone has them off the top of their head.

DR. SALIVE: But would I be correct to say those might be less likely due to chance?

DR. KIMMEL: I think that certainly is a reasonable assumption.

DR. FARBER: I the in the analysis that we did when there was a dechallenge to rechallenge we probably gave that AER a high probability.

DR. KIMMEL: The problem with --

DR. FARBER: Frankly, there weren't many of them.

DR. KIMMEL: It a small number. The problem with dechallenge of course alone which was a much larger number is, for adverse events like MIs and strokes, the fact that you don't have another -- there is with dechallenge from an MI. So it's hard and I don't think.

DR. SALIVE: The challenge from the product is what I was speaking of.

DR. KIMMELL: Right. But if you stop the products and then don't have another MI, does that mean that the product was the MI. I mean, in other words, for those types of acute events that happen in isolation at a particular time, I think obviously dechallenge is not particular helpful. And I don't know of any cases of rechallenge of recurrent MI or strokes.

DR. JONES: Dr. Farber.

DR. FARBER: Page points out to me that in most of those dechallenge/rechallenge situations it was

generally an allergic phenomena that was reported in the AER.

DR. JONES: Dr. Burstein.

DR. BURSTEIN: Aaron Burstein, Clinical Center at NIH. I have a question for Dr. Page regarding some of the kinetic you presented, specifically the study of White and colleagues. Could you just clarify for me the specific product that was tested because I know that some of the studies have looked at single entity products versus products that also contain herbal therapies that contain caffeine some of the kinetics may differ depending on the product.

DR. PAGE: Right. Let me get my data on the study. Okay. The White study did pertain to the use of a dietary supplement ma huang. It was the commercial product called ma huang.

DR. BURSTEIN: I believe that the authors in that study refer to it as a single entity product in the same group, later goes on to study combination products with caffeine.

DR. PAGE: That's correct.

DR. BURSTEIN: So, I think that is important to point out that that slow absorption rate has only

been documented for the single entity product and when you administer these products with caffeine the hypothesis is that the caffeine actually speeds to rate of absorption such that there's really no difference between those combination products and synthetic ephedrine.

DR. PAGE: You probably are right. That's the reason I didn't really emphasize it. We really know that much about the absorption. So I think call them all the same is probably a conservative approach on it.

DR. JONES: Dr. Schwetz.

DR. SCHWETZ: I have three questions, two quick ones for Dr. Hutchins. How were the 22 deaths selected for your review? And are the results of your analysis published or reported someplace that they could be put into the record?

DR. HUTCHINS: The 22 deaths were included in that whole group of AERs that we reviewed and were selected from that.

DR. KIMMEL: I think they came from -- it was in March of '97.

DR. FARBER: The 22 deaths were the total deaths in the 276 AERs reported out about Food in Drug in March of this year. They were not selected, they

were the total number of deaths in the AERS.

DR. SCHWETZ: Yeah, I thought I remembered the number 7 deaths from the information this morning. Are those seven that were referred to this morning among these 22?

DR. HUTCHINS: It would be my assumption that they were, but I do not know for sure.

DR. KIMMEL: It was all deaths included since March 1997, if I'm correct. I don't recall specific I recall seven in which the reviewer felt that they were attributable amongst all deaths. We didn't look at just the attributable, we looked at all -- all deaths that were provided by FDA from March '97, in fact, I think it went all the way through 1999.

DR. SCHWETZ: And my other question is whether not there is more information that can be submitted to the record regarding your evaluation of these death records?

DR. HUTCHINS: I have written a brief report on the first 11 cases that I looked at. I haven't completed that for the next 11, but I would be happy to submit that in a few days.

DR. SCHWETZ: I have one other question that has to do with the denominator. Thank you Dr. Hutchins.

Several people have made reference to the fact that there are several billion servings per year but how does that translates into the denominator?

DR. KIMMEL: The calculation was done on the basis of the data in the survey which has been submitted to the docket was total number of servings plus we were able to calculate average serving sizes an average servings per day. So, we could essentially assuming normal use, assuming use according to directions, we calculated the average person time. And I can show you details if you would like, but it's an estimate of person time from person days.

DR. SCHWETZ: I don't need to know but I'd like to see it if you have it for the record so that you can calculate how many people are one-time users how many people are multi-time users, what else do they use?

DR. KIMMEL: You can't tell that from this at all. This is purely an estimate of number of person days exposed based on total exposure and total doses and amount of dose per day. It is just like you would use prescription records for a prescription drug in doing the same type of assessment with AERs where they try to estimate the number of events or number of prescriptions written.

There is no individual patient level data or person level data. There's not information on time and duration, so we can's assess that all. This is purely a one slice total amount of exposure over the 22 months as the denominator with the number of events in those 22 month periods as the numerator.

DR. JONES: Dr. Philen, did you have a follow-up question?

DR. PHILEN: No.

DR. JONES: No? Okay.

One question then from me. I comment AHPA for taking some effort toward labeling dosing recommendations and so forth. I wanted to know what the basis was for the 25 milligrams, four times a day, recommendation, is that drawn from related compounds, has there been a controlled clinical trial, dosing studies done in that respect?

AUDIENCE PARTICIPANT: If you please, I'm council to the Ephedra Committee of AHPA, and that is actually kind of a legal question rather that a scientific question. I helped put the panel together and I know they probably don't know the answer to that question because it was done several years ago. I know that Michael McGuffin, President of AHPA, is going to talk tomorrow, and I would respectfully request we wait

until he talks, he can address that issue.

DR. KIMMEL: But I can give you a little information from hot scientific standpoint in terms of my interpretation of this being reasonable. Over-the-counter ephedrine is 25 milligrams up to six times a day, total dose of 150 milligrams. This is last in total ephedrine alkaloids. In addition Dr. -- I'm sorry if I pronounce it wrong -- Enchiosa, who wrote a report for FDA did comment that the relative potency for instance of pseudoephedrine is less than ephedrine and she actually gives an example, and I don't remember which product it was, but if you add up total ephedrine alkaloids in the product it was 34 milligrams, but the ephedrine equivalent of nd over-the-counter product would be 11.75. So at least my personal feeling is that this is not as high in fact essentially lower than the over-the-counter products. So for my own sort of personal clinical point I think it's total reasoning.

DR. JONES: That is really my reason for asking is, was it drawn from those sorts of data as well as evidence.

Other questions from the panel?

[No response.]

DR. JONES: Questions from the floor? Please come to the microphone and identify yourself please.

MR. REINHART: Yes, Jeffrey Reinhart, People for Pure Foods. I have a question for Dr. Schwetz.

DR. JONES: The panel that is presenting is the panel to which you should address your questions unless Dr. Schwetz's question is not clear and you would like him to restate his question. The information presented by the panel as part of the meeting is where we would specifically like to seek clarity.

MR. REINHART: Looking for clarity, has your group done, or do you intend to do any formal rigorous meta analysis of peer reviewed published literature? It seems that meta analysis criteria are appropriate here.

DR. KIMMEL: I can speak to the method of meta analysis. Per case series I would call it a summary, there's nothing to meta analyze per se. Meta analysis really are applicable to randomized trials.

MR. REINHART: So you need double blinds.

DR. KIMMEL: We did -- one of our consensus statements is that there should be considerations for other studies. If DHHS and NIH and others feel that some types of summary estimates are, for lack of a better term meta analysis would be helpful I think that would be worth a trial, although I would caution that I

think meta analysis for case series or essentially useless.

MR. REINHART: Backing up from meta analysis could, you characterize your method of analysis within the context of the FDA's Doctor nonsignificant scientific agreement? Would you say you for fulfilled those criteria?

DR. KIMMEL: Could you restate the question? I'm not quite sure I understand it?

MR. REINHART: Did your analysis fulfill or come reasonably close to the FDA's doctrine of significant scientific agreement?

DR. KIMMEL: I'm not sure which analysis and I'm not sure what FDA says is the definition of significant scientific agreement so I can't answer maybe someone else on the panel can. I was not aware that there is a definition of "significant scientific agreement."

MR. REINHART: Thank you.

DR. JONES: Next question, please.

MS. FUGH-BERMAN: Adriane Fugh-Berman, National Women's Health Network. There are a number of reports and in the medical literature that were not included in the analyses I have seen this afternoon. But I'm particularly curious about one case that was

left out of the Dr. Karch's report on cardiomyopathies. And I was wondering, Dr. Karch, why you left out to the case of the 23-year-old that was published by Thiaharates which I know you're familiar with since you wrote a letter to the editor about it.

DR. KARCH: Well, I left it because it's not a cardiomyopathy. It is a florid myocarditis. I finally got a chance to examine the slides and to any cardiac pathologist who has seen them is pretty clear, and I've shown them to other cardiac pathologists. It's garden variety myocarditis, and that's not cardiomyopathy and that's why it's not included with the list, in spite of Dr. Theohardies paper and, of course, he's not a cardiac pathologist.

MS. FUGH-BERMAN: Right, but it had been shown to a cardiac pathologist. And I would like to correct the former speaker. I believe it was Dr. Page referring to the same case, that 23-year-old did not have a history of cardiac disease. And I have the report with me if you care to see it.

DR. PAGE: Well, I would just indicate that I have reviewed the medical records, and a I don't think you're right, but I'd be happy to take a look at what you've got to offer.

I did have that listed, by the way, as my

number one case as you probably saw.

DR. FARBER: There's another interesting aspect about that case. When the Food and Drug investigator went into the young men's apartment to try to pick up samples, the only open bottle that he found, and we maybe sort of logically assumed that that was the bottle that he was using at or somewhat before his death that that sample was taken off by a Food and Drug investigator and analyzed and shown to only contain pseudoephedrine and not ephedrine whatsoever. And this is described as an ephedrine-related death, calculations are made by the professor from Tufts in regards to some very almost negligible or almost insignificant levels found in the urine of ephedrine, pseudoephedrine was not found in the urine. One wonders where the ephedrine is coming from in that particular urine sample. It is an interesting case.

MS. FUGH-BERMAN: I admit to being confused here. The product that was implicated was Twinlabs Ripped Fuel which his sister said he had been taking once or twice a day in recommended dosages. Is that the product that you're saying contains pseudoephedrine and not ephedrine?

DR. FARBER: It's in the AER record. It's plain and simple, the sample was picked up and analyzed