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EPHEDRA: WHO IS PROTECTING THE AMERICAN CONSUMERS?

HEARING

BEFORE THE

OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING, AND THE DISTRICT OF COLUMBIA SUBCOMMITTEE

OF THE

COMMITTEE ON
GOVERNMENTAL AFFAIRS
UNITED STATES SENATE

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EPHEDRA: WHO IS PROTECTING THE AMERICAN CONSUMERS?

TUESDAY, OCTOBER 8, 2002

U.S. SENATE,
OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING,
AND THE DISTRICT OF COLUMBIA SUBCOMMITTEE,
OF THE COMMITTEE ON GOVERNMENTAL AFFAIRS,
Washington, DC.

The Subcommittee met, pursuant to notice, at 10 a.m., in room SD–342, Dirksen Senate Office Building, Hon. Richard Durbin, Chairman of the Subcommittee, presiding.

Present: Senator Durbin.

OPENING STATEMENT OF SENATOR DURBIN

Senator DURBIN. Good morning. This hearing will come to order. I am pleased to welcome you to today's hearing before the Senate Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia, focusing on "Ephedra: Who is Protecting the American Consumer?"

Dietary supplements are safely consumed by millions of Americans every day. I, myself, take a variety of supplements, multi-vitamins, folic acid, all the things that I think are going to make me live forever. I hope they do. For the vast majority of dietary supplements, there are few reports of harm. For some, there is strong scientific evidence that they provide a health benefit.

However, that is not the case for the supplement ephedra, which is the focus of this hearing. The Food and Drug Administration reported that in the year 2001, 42 percent of the total number of adverse event reports, known as AERs, received for all dietary supplements by the agency were for one supplement, ephedra. In some years, such as 1996, the percentage was as high as 70 percent, as this chart indicates.

Particularly alarming was the fact that many of these ephedra adverse events were suffered by young people. The HHS Inspector General noted that 60 percent of the alleged injured parties by ephedra were under the age of 40. Furthermore, if you look at some of the most serious adverse events reported to the FDA for dietary supplements, you find that ephedra is disproportionately represented, as the chart indicates. Seventy-eight percent of myocardial infarction AERs were for ephedra products. Eighty-one percent of stroke AERs were for ephedra products. Sixty percent of the deaths were for ephedra products.

Independent scientists without ties to the industry have analyzed these adverse events and reached disturbing conclusions. A study

published in the well-respected *New England Journal of Medicine* in the year 2000 reviewed ephedra AERs received by the FDA between June 1, 1997, and March 31, 1999. The study concluded that 31 percent of the reported adverse health outcomes were "definitely or probably" related to ephedra use, and an additional 31 use were deemed to be possibly related to ephedra use.

We are not necessarily talking here about people taking a higher than industry recommended dose. A study in the Mayo Clinical Proceedings in January 2002 reviewed the cases of 37 patients who suffered adverse cardiovascular events, specifically sudden death, myocardial infarction, or stroke, and found the cardiovascular toxic effects of ephedra were not limited to massive doses. Of the 37 patients in the Mayo Clinic study who experienced one of the health problems I mentioned earlier, 36 of the 37 were using amounts no larger than what the manufacturer recommend—36 out of 37. That means that over 97 percent of the adverse health events occurred in individuals taking ephedra at or below the manufacturer's suggested dose.

It is studies such as these that have led so many health professionals to conclude that ephedra is not a safe product and should be taken off the market. We will hear later this morning from Dr. Ron Davis, representing the American Medical Association. I do not think anyone is going to suggest here the AMA is a radical group with an axe to grind. They are known for championing causes which are based on science. Yet, the AMA has forcefully called on the U.S. Government to take ephedra-containing dietary supplements off the market.

We are also going to hear from a premier health consumer advocacy group Public Citizen. Dr. Sid Wolfe will discuss why Public Citizen has also called on the government to protect the American people from these dangerous ephedra products.

We will hear from those who have taken action to protect the public. Dr. Howard Beales will testify on behalf of the Federal Trade Commission about the enormous job the FTC is forced to do to police deceptive advertising of ephedra products that some would have you believe are natural and safe.

Bill Jeffery of CSPI in Canada will tell us about Canada's efforts to protect their own citizens. On January 9 of this year, the Canadian Government issued a warning, a warning which this government has never issued, about certain herbal ephedra products sold for the purpose of weight loss, body building, or increased energy. That warning urged Canadians to avoid the products because they may cause "serious, possibly fatal adverse effects when combined with caffeine or other stimulants."

When we hear from the first panel, when we hear from the parents of Sean Riggins, you are going to understand how children do not have to drink coffee to get caffeine with these ephedra products.

Many of the ephedra supplements recalled by the Canadian health authorities can be found on the shelves of stores across America. These are examples right here of products containing ephedra. I can tell you this. You go into any gas station where I live in Central Illinois, where the Riggins family is from, and you will find next to the cash register, there for kids to buy, all sorts

of ephedra products. You go into a convenience store, a gas station, they are everywhere and kids are buying them, sometimes with tragic results.

For the record, there are several other countries, such as Britain and Germany, which have taken action to protect their citizens, as Canada has. A variety of athletic organizations, the International Olympic Committee, the National Football League, the National Collegiate Athletic Association, have banned ephedra-containing dietary supplements.

We are going to hear from Frank Uryasz, representing the NCAA. He will testify that in spite of this ban, a 2001 NCAA study found 4 percent of 21,000 athletes, about 850 of them, who completed the confidential survey, had used ephedra in the past 12 months despite the ban. Even more disturbingly, this number has increased since the ban at the NCAA went into effect in 1997, particularly among women's teams. According to the study, most athletes, who reported using ephedra-containing products, started using them in high school. The NCAA has also called on the FDA to more tightly regulate ephedra products because of the harm they can cause to athletes and others.

One young athlete who started using ephedra products in high school is tragically no longer with us today. You see his photograph here. Kevin and Debbie Riggins of Lincoln, Illinois, are going to testify about the tragic death of their 16-year-old son, Sean, who died on September 3, just over a month ago, of a heart attack after taking an ephedra product known as "Yellow Jacket." Yellow Jacket, incidentally, is also the street name for a narcotic. Coincidence?

My heart goes out to them. When I read this in the local newspaper, the *State Journal Register,* about the loss to their family, I could not believe it. We just had a hearing on this issue, and here it was hitting close to home with a healthy young man, just starting his high school year, looking forward to wrestling and football and all of those sports. I want to thank them for coming here. It takes real courage for them to stand up and tell their story so soon after their loss.

But we need to remove these products from the market so other families like theirs do not see their loved ones' lives cut short for the sake of an energy buzz or the loss of a few pounds. I am looking forward to today's testimony to help us better understand this issue and the responsibility we have to the American people.

After the last hearing, I sent a letter to Secretary Thompson at the Department of Health and Human Services. I have spoken to him on the phone several times about this issue. He has assured me he is looking at it seriously. Unfortunately, he could not be here today because of a trip to Afghanistan, which he had promised long ago, and I understand those things. Conflicts are inevitable for busy people like the Secretary. But I can tell you that letters are not enough, and telephone conversations are not enough. We want to find out today whether our government is going to take any action to protect the people who are being victimized by this drug across America.

Our first panel of witnesses are Kevin and Debbie Riggins of Lincoln, Illinois, parents of Sean, and also joining them is Charles Fricke, who is the Coroner for Logan County.

Mr. and Mrs. Riggins, I appreciate your willingness to appear today and publicly share your personal experience. It is customary in this Subcommittee to swear in the witnesses, so if you would not mind, remain standing.

Do you solemnly swear the testimony you are about to give is the truth, the whole truth, and nothing but the truth, so help you, God?

Mr. RIGGINS. I do.

Mrs. RIGGINS. I do.

Mr. FRICKE. I do.

Senator DURBIN. Thank you very much, and the record will indicate that the entire panel has answered in the affirmative.

Mr. Riggins, would you like to begin?

TESTIMONY OF KEVIN RIGGINS,[1] LINCOLN, ILLINOIS

Mr. RIGGINS. Yes. I just wanted to thank you, Senator, for bringing us to Washington so we can tell this story. I greatly appreciate it.

I will begin by introducing myself. My name is Kevin Riggins. This is my wife, Debbie, and the young man in the picture is our son, Sean. We are here to tell his story. You have my written statement. I am not going to read that word for word. I just want to tell you a little bit about my boy.

Sean was a very healthy young man. He started playing hockey when he was 7 years old, first grade, when we lived in Peoria after I separated from the service. He then got into the martial arts and he was quite the martial artist. We attended tournaments all over the Midwest, Indianapolis, Wisconsin, Peoria, Decatur, Bloomington, Springfield, all over the place. He has a stack of trophies at home in his room. He achieved the rank of red black belt.

Later on, though, his passion turned to team sports, wrestling and especially football. He was quite passionate about the game of football. Again, my son was in outstanding condition. He lifted weights. He exercised constantly. He would ride his bike, before he got his driver's license, all over Lincoln, down to the creek to go fishing and swimming and that sort of thing, and that is why when my son passed away and they told us that he had died of a heart attack, I had no idea what to think. How does a 16-year-old boy that active die of a heart attack?

That is when we spoke to Chuck Fricke. He called us after the visitation and told us that they had found a substance known as ephedrine in Sean's system, or that the indications pointed toward that being the case.

We started doing some investigating, along with Mr. Fricke. The Lincoln Police Department started investigating with some of the kids, Sean's friends, his teammates, and we found out he was taking what is known as Yellow Jackets, which is an ephedrine product. This is over-the-counter. You can buy it in the gas station. They are about $1.50 for three pills. That is pocket change for these boys.

They are using it on the football team to enhance their performance, as it claims in the ads and what not. They are using it, the

[1] The prepared statement of Mr. Riggins appears in the Appendix on page 53.

wrestlers are using it and basketball players. We have got young girls who are using it to try and help them lose weight.

None of these kids that we have talked to—and I know my son never used drugs—none of these kids use drugs. They are not drug users. They are not abusers. They do not smoke cigarettes. Sean never smoked cigarettes. He never smoked marijuana. He did not take drugs. Mr. Fricke can bear that out. He was passionate about not taking drugs. He had a couple of friends that did smoke pot and he was constantly after them about stopping, because he saw his grandfather die of lung cancer and he did not want to see that happen to anyone else.

The problem with ephedra, in my opinion, is that these kids do not realize that it is a harmful drug. Whether they call it an herbal supplement or a dietary supplement, that is just semantics. It is a drug. Garlic is an herb. Bay leaf is an herb. But I have never heard of someone dying from bay leaf. This herbal supplement killed my son and I am just afraid that this can happen again if these kids have access to this kind of stuff on a daily basis at the gas station for a buck-and-a-half.

They put it in flashy packages. They have flashy advertising. They gear it toward young people. It is not geared toward a 40-year-old man that works 40 hours a week. This is geared towards younger people.

What I think is that we need some type of regulation regarding ephedra and like products because, again, this can happen again. If a 16-year-old cannot get to it, it is not going to happen. They cannot take it. So we should make it, at least I think where if you are 18 and younger, you cannot get to this product. If a grown man wants to take it, that is his choice. If a grown woman wants to take it, that is her choice. But a child should not be able to make that choice.

These companies that market this should have to be held accountable, because I do not feel that you should aim something at a child. You can put all the warning labels you want on them, but cigarettes have had warning labels on them for how many years and people still smoke.

It is very simple. We can just effect a regulation making it illegal to sell to kids. We enforce that regulation and we do not have to go through this again, because I do not think that I could do it again.

Senator DURBIN. Thank you, sir. Kevin, you made a point of pointing with pride to this jersey that you brought from Lincoln. Why don't you tell me a little bit about the jersey.

Mr. RIGGINS. Sure. This was my son's practice jersey. Obviously, he was number 51. We put this out at the suggestion of one of his friends at his visitation and all the kids and teammates and what not came and signed this jersey. A good friend of mine is going to build a display case for it so we can have this displayed in our home. We also have big posterboards that the kids signed because the shirt was not enough. We had close to 600 people come to our visitation to see my son. That is a testimony to him, not to me, and a testimony to the people that cared enough. That is what this jersey is.

Senator DURBIN. Thank you. Debbie, can you tell us a little bit about your thoughts on this?

TESTIMONY OF DEBBIE RIGGINS,[1] LINCOLN, ILLINOIS

Mrs. RIGGINS. My feelings on the subject. I did not know the dangers of this product until September 3. I did not realize what it could do, what its potential was, and it is being mismarketed in a way that it is only there for somebody to make money and they do not seem to care who they are hurting.

I brought a couple of letters from some of the students who went to school with Sean.

Senator DURBIN. You might describe for the record here, Lincoln, Illinois, the size of the town, so people get an idea of where we are talking about—I know the answer, but I am going to ask you to put it on the record. We are not talking about big city here, are we? What is the population of Lincoln?

Mrs. RIGGINS. About 17,000.

Senator DURBIN. Seventeen-thousand.

Mrs. RIGGINS. We live about three blocks from the high school and on the other side of the high school, there are corn fields.

Senator DURBIN. Small town America.

Mrs. RIGGINS. A small town. People ride bikes. Even the grownups ride bikes everywhere. We have one theater. It is a place where everybody can go to the store and they know somebody there.

Senator DURBIN. So I just want to make the point that this product, this type of product is reaching down to all levels of America. This is everywhere.

Mrs. RIGGINS. Oh, yes. It is right at their eye level. As soon as they are standing in line for something, they see it right there and they are going to pick it up and they are going to look at it. As long as it has got the flashy colors on it, and they test market those colors to see who is attracted to them. If they are going to spend that kind of money on advertising and displaying it, they have got to make some money—replace that money somehow. Kids apparently are easy targets.

Kids take it to get hyper so that they can stay up late, so that they can stay awake the next day, some of them to study late because they have got a big test the next day, or they just did not get enough sleep the previous night. This one kid stated that anybody can do it and it is cool to hear a friend say, "Hey, feel my heart. I am speeding right now." One of the students actually wrote that. This other student says, "I have had experience with Yellow Jackets and Stackers in the past years," as a sophomore.

Students told us that at the end of eighth grade, it became popular, even more so with the freshmen year. One said, "Most people and my friends took them because it gave them enough energy to sit in a desk all day without feeling really tired or bored. It made the day go faster." Another reason given for using ephedra, a more serious one was that it made them feel as if they were on speed. People would take several at a time to keep them wired and

[1] The prepared statement of Mrs. Riggins appears in the Appendix on page 55.

pumped up all day long, and I know or have heard some people went as far as snorting them.

Another student wrote: "I took one pill before each meal and I took these for about a week and then I quit. I wasn't losing any weight and I was always sick. I had terrible headaches that took forever to go away, and in a while, I would be short of breath or I would have this pain that hurt in my chest. After I stopped, I tried the Stacker, too, and it had the same effects, but with more pain."

So even the kids are learning, but unfortunately, they are learning at a price. We do not know yet if it is a long-term effect, if it is one dose that is too much, is damaging them. But we need to find out. We need to find out what is safe, and if it is safe. I do not think it is. They took my only son and won't bring him back.

Senator DURBIN. Debbie, thank you for being here. Chuck Fricke, you have the responsibility as Logan County Coroner. You might tell us a little bit about what that responsibility is for those who are not familiar with the office and then tell us what you found in this case.

TESTIMONY OF CHARLES FRICKE,[1] LOGAN COUNTY CORONER, LINCOLN, ILLINOIS

Mr. FRICKE. First of all, the coroner investigates any death that is not a natural cause of death and he determines with his investigations the cause and manner of an individual's death. Cause of death in most instances is determined by a forensic pathologist that does toxicology studies as well as external examinations of the individual.

In this particular case, we were notified by the emergency hospital, Abraham Lincoln Memorial Hospital, that a 16-year-old boy had died. You do not hear about 16-year-olds dying of myocardial infarctions. At that time, we did not know what it was, but upon examination by the pathologist, he came back with that, and I says, "due to what? I mean, over-exertion? What is it?" He says, "Well, please, help us out in your examination externally by investigating."

I had the Logan Mason Health Department do an investigation where the boys had been on the weekend, over at Clinton nuclear power plant. We thought maybe something was in the water that he had drunk or been exposed to. One of their witnesses told us that he was Yellow Jacketing and the group was jointing. We asked what that was. I had to investigate, like the family and most people, to know what that was.

They told me that Yellow Jackets, as you have pointed out, come in small little packages, or in this particular case, ephedrine is in a pack of 60. The label tells you that it should not be sold to minors, that selling to a minor is prohibited. It is a dietary supplement and extreme energizer. This particular product says, "Do not sell to minors. Distribution of this product requires a DEA license."

I asked the distributors at the Quick and Easy what that meant, how they enforced it. They did not know. They did not have a license for it. They do not prohibit sales to minors. In fact, I had a

[1] The prepared statement of Mr. Fricke appears in the Appendix on page 56.

12-year-old go in and buy these products for me. My State's Attorney says that we cannot prohibit the sale of these products even if the warning says so. It is a manufacturer's label, mislabeling, to me. They think they are buying something illegal.

In the testimonies that Debbie has, it says that they would go in and steal them because they did not think that they could buy them, so they were starting to steal them. Then they found out they could buy them legally. Now they are buying them in threes. Some are buying them in groups of 60.

We had the city detectives, police department of Lincoln go out to the high school to do investigations with the superintendent, the principal, the athletic department and all sports. It was a shock to them, because they did not know what ephedrine was. Only one of the coaches understood what it was. They wrote a nice letter on behalf of the children, the consumers at the high school. They have started a program and have made brochures about the ill effects of ephedrine. They are trying to get the word out, because as you and I were novices in this just weeks ago, we are finding out that the schools and the kids are not novices in this.

How does a 16-year-old die of myocardial infarction? It was not just a mild myocardial infarction. I had to ask the pathologist what that meant. Troponin, which is an enzyme, a specific marker to the heart, was at 100 level, the number 100. You and I as adults have troponin levels of one or two on a normal day. The troponin in your heart tells it to keep beating. When you are having a heart attack at 50, 60 years old, 70 years old, it would be marked at four to five. Think about it. Sean's was at 100. The heart is racing so fast, it just kind of could not do anything. He could not pump the blood fast enough and that is the way he had a heart attack.

We have put out warnings in the newspapers. We have contacted the schools. The schools have done their part about notifying their athletes. We want to notify athletes and consumers everywhere, not only in Central Illinois, all of Illinois, and the entire Nation so that you can regulate this product more tightly so that the consumers understand what they are buying when they buy it.

The doctors that I have contact with, not one of them had a good word—I am sure there are always therapeutic values that ephedrine is used for under controlled circumstances, under doctors' care, but we cannot take the 99 percent of the kids that are using this and use them as examples for the one or two times that it is healthful under a doctor's supervision.

Senator DURBIN. Thank you very much. Let me ask you this, Mr. Fricke. You stated this in your written testimony, but I want to make sure it is a matter of the spoken record, as well. Do you believe that the death of Sean Riggins is consistent with his having taken these ephedra products?

Mr. FRICKE. Let me read exactly, word for word, from the forensic pathologist. "It is our opinion that the acute myocardial infarction in this individual is consistent with the effects of ephedrine. No other anatomic, structural abnormalities of the coronary arteries sufficient to cause myocardial infarction was identified in the autopsy." And with his health records and our investigations, it proves that out.

Senator DURBIN. Of course, Kevin and Debbie have made that case, too. This was not only a healthy young man, an active, athletic, vigorous person who was leading a very active life. So that certainly bears it out.

You have the smaller version of Yellow Jackets with you, and as I said earlier, you can just walk into any gas station in our part of the world and you are going to find these hanging all over the cash register for the kids to see. Then you take a look at one of these. Now, this is their big deal. This is their $31.95 jar of Yellow Jackets that they have for sale.

Do you know where they put the warning label on this, incidentally? You think it might be out here where you would see it. No. You have to strip back the label and you have to read the back of the label, and I am sure a lot of 14-year-old kids are doing this, right, stripping this label back so that they can read this faded printing on here that says, "Keep out of reach of children." What a joke!

We asked the people from this company to come forward today. You will be shocked to know they could not make it. We do have a representative from the industry here, and he will be speaking to us later.

But I have to go back to Debbie's point. At what point do you draw the line here at making money? If you are peddling a product to kids and you know it, and incidentally, this warning label says, "Sale to persons 17 years of age or younger is prohibited in Texas." Do you know why? Because 20 States, I guess roughly 20 States have decided the Federal Government is ignoring this problem and the States are starting to impose standards because our Federal Government, our FDA is ignoring this problem.

Canada has responded. The AMA has responded. Sports organizations have responded. But the American Government has not responded. And despite letter after letter, we have no action on this. So the States are taking it in their own hands. I cannot think of another time when we have dealt with this, where States have decided they have to regulate the sale of a product because the Federal Government is so much in the grips of this industry that they are afraid to protect the American consumer.

Kevin, did you and Debbie see any indications of this heartbeat, this racing, the speeding up of his heart? Did Sean ever talk to you about this at any time?

Mr. RIGGINS. No, never. In fact, Sean was the type of boy—he was a typical teenager. If he felt bad and he had something he wanted to do, he probably wouldn't tell you about it. If he had a little bit of a cold or a stomach virus, if he wanted to go out and go fishing that day, he was going to go fishing. He would not tell you about that sort of thing.

A lot of these kids that we have talked to, they did not attribute their symptoms initially to what they had taken. They just thought that they were tired or they were catching a cold or a flu or something like that. They had—most of them had, no idea that this product was what was making them feel bad.

Senator DURBIN. On the day of his death or the day before, was there anything unusual about his behavior or anything he said to you that, now that you look back on it, was a warning sign?

Mr. RIGGINS. There was nothing more than he had a headache—and this is prior to our investigation of this product and this type of thing—he had a headache and his stomach was bothering him. That has happened, in 16 years, that happened who knows how many times.

Senator DURBIN. Debbie, do you know anything——

Mr. RIGGINS. He went to the football game the night before, on Monday night, and like Kevin said, he had to go to the football game and he slept underneath the bench. How many times do you know kids that would do that at a football game? Something was happening, but we didn't know. We just thought it was bronchitis or some flu going on. He laid down during the game, or at least in the first half. He got up the second half and met with—when they go during the halftime—and he met with the team and then he came back and sat on the bench.

He had his car with him at the time, so he wanted to drive home, so he drove home, said his head hurt, his stomach was a little upset, so he was going to go to bed. He took a Tylenol, I believe he took a Tums for his stomach, and he went to bed that night. I had to work the next morning. That is the last time I saw him.

Senator DURBIN. Chuck, you have gone around the community there now and I know you have done an awful lot, and thank you for that, because your speaking out has made a difference. It is starting to get the word out, at least in our part of the world, about the danger of these products. What is the prevalence? How frequently do you find that young people are using these?

Mr. FRICKE. WAND, a TV station out of Decatur, did a survey and I called them this morning. They said they had 250 calls in 3 days regarding this and it was two-to-one that had ill effects with ephedrine.

They also had a young lady that had taken it just one time, from Effingham, and she went to bed and she woke up 4 days later at Carl Clinic at Champaign. She had seizures and had gone into a coma for 4 days, and her mother stood there and helped her get through this. She was lucky to survive. She sent a note to us, Ms. Spitz, wanting us to tell her story and to say that it does not take a multiple of this drug. It does not take an active athlete running in the 90- and 100-degree temperature. It was a house mother that went to work, went to the grocery store, came home, went to bed not feeling well, and had taken just one of these supplements.

Senator DURBIN. Now, if you take one of these with caffeine, it really just aggravates it, doesn't it, makes it worse.

Mr. FRICKE. If you look on the Yellow Jackets, it has 300 milligrams of caffeine. A Stackers has 200 milligrams. Some of these children that I talked to in my investigation, they are tired, they are exhausted, they have gone through 6, 7 hours of school. They have had a school lunch. They have gone through 3 hours of football practice. They are tired. They are exhausted. And now they have activities, they have homework at night. They are too tired to eat.

They go to the local Quick and Easy. They pick one of these up. They buy a product, if I may mention, products that contain caffeine in them that compounds the injury.

Senator DURBIN. Mountain Dew.

Mr. FRICKE. Mountain Dew, Code Reds, and I am not trying to be negative to those products. I have drank those products, too. But in combination with ephedra, and these children do not know it, adds to the dangers. There is also an adrenaline rush drink out there that they use.

The young lady that prohibits them in Mount Pulaski is on a voluntary basis, says that—and she knows that she has to tell these to anyone, but she used these products herself in college and she knows the ill effect. But her company tells her to put it out front, so she has taken it from the front cash register and put it behind her. Now you have to ask her to get it. And she puts out a warning label that says on these warning labels that you can only sell two per person per day, and she makes them show their ID, so it is very inhibiting when you do that.

But other places that I have been, five, six different places, 12-year-olds go up and buy this, and I think it is a big rush because they get their heart racing. They do not know the dangers—when you are 16, you do not think you can die until you are 60, 70, 80, of old age. They become bulletproof and they think they are. And unfortunately, I have the unfortunate task of going up to families like the Riggins and telling them that their son died of a myocardial infarction due to a product that this government does not regulate, and we need to.

Senator DURBIN. Chuck, when it comes to activities in your community and nearby, public education is part of this, but is there going to be any kind of follow-up effort at the schools to talk about this problem?

Mr. FRICKE. I have talked to the superintendent of the Lincoln Community High School and he has invited the parents and myself to come out and not only just give an assembly to the entire school, but I thought that on an individual basis or on a smaller scale, it would be better. So I want to take the days and take the opportunity to talk to the gym classes so that you can break that 1,200 students down to 30 and 40 at a time, talk to them individually, the athletic departments.

I want to talk and educate the coaches on this, and not only in Lincoln, but I have to know that it is happening in Springfield at the schools, at Litchfield, at Bloomington, at the small school levels, so that the athletic directors do not wake up themselves in the community and find out and then they have to start where we started. We started as novices and we are not going to let things sit and go unabated.

We are going to reach out to these people. We have interviews when we get back because we feel very strongly that we want to get the word out. We do not mean to have an overkill on this, but the more we can do it—this has been in the paper almost every day, trying to put warnings out. We are putting it out on TVs, on radios, and in the newspapers, and anything you can do to help us on a local basis would be appreciated.

Senator DURBIN. This is a sad thing for me to say, but I am going to say it. You are doing more to protect the people that you represent than our Federal Government is doing to protect people across America.

Mr. FRICKE. We speak for Sean today because he can't speak, and as the coroner, we investigate those things. He told us a story. We had to listen to him. Not many people take that time to listen, and we listened to what he had to say, and these are his words. Today, this is for him.

Senator DURBIN. Thank you.

Kevin and Debbie, this had to be tough. When we invited you, we didn't know if you would do it, but as you said to me before this hearing, you have got to do this for Sean, got to get that message out so that some other family does not lose their only son, as you have. I hope that your being here today and I hope that fact that some people are watching this and following it will mean that they may tonight pull their daughter or son aside and say, have you ever heard of these things, Yellow Jackets or ephedra? Are any of your friends involved with them? I mean, this is as insidious and harmful and dangerous as a lot of drugs that are on the street that we are warning kids, to just say no to. It is time for them to just say no to Yellow Jackets and just say no to these products because it can kill them.

Your coming here today drove that point home in a way that all the witnesses in the world couldn't. I am saddened for your loss, but I admire your courage that you can tell this story and try to save some other lives across America. Thank you for being here.

Mr. FRICKE. Thank you, Senator, very much.

Senator DURBIN. I now want to just take a few minutes as this panel is leaving the table to review an interesting report that Congressman Henry Waxman's Special Investigations Division staff prepared, working with my own staff. This is the first independent analysis of the adverse event reports that Metabolife finally has given over to the Food and Drug Administration.

Chart 1 here, the Durbin-Waxman staff reviewed all 14,459 computer images that Metabolife provided us. This constitutes all the adverse event report records that Metabolife, and I have some of their product here before us, received since 1997, over the last 5 years. A new, database was created for analysis and staff individually reviewed each record. Records that indicated that consumers had suffered a particular serious health problem were put into this database.

The serious health problems analyzed were those already identified as being caused by ephedrine. They included cardiac symptoms, including heart attack, chest pain, arrythmia, racing heart, high blood pressure; neurological symptoms, including stroke and seizures; psychiatric symptoms, including psychosis, anxiety, and mood changes.

The Metabolife records include over 1,900 reports of significant adverse reactions to Metabolife products. Second chart here, Metabolife's adverse event reports. What we see is that they include 3 deaths, 20 heart attacks, 24 strokes, 40 seizures, 465 episodes of chest pain, 966 reports of heart rhythm disturbances. In addition, the reports contain hundreds of consumer complaints of high blood pressure and disturbing psychiatric symptoms, such as anxiety, mood change, or psychosis.

In at least 46 instances, consumers reported that they required hospitalization following use of Metabolife products. In at least 82

additional incidents, consumers reported they needed emergency room care after using these products. In numerous adverse event reports, consumers told Metabolife their doctors had determined that Metabolife's products had caused the adverse health effects complained of.

The Metabolife records indicate that many of the significant adverse events involve consumers who were young, in good health, and taking the recommended dosages. The next chart, this relates to adverse effects reported by healthy young people at recommended doses. Metabolife has asserted that adverse events don't occur when healthy individuals follow their recommended doses. The actual adverse event reports, however, include many reports of significant health effects in healthy consumers taking recommended doses. Among the most significant are heart attacks, seizures, strokes, and psychosis.

Over 90 percent of the reports where dosage information is noted, consumers were taking the dosage recommended by Metabolife and still suffered these results. Among the significant adverse event reports where age is noted, over 50 percent of the reports involved consumers under the age of 35. In hundreds of cases of significant adverse events, the consumers involved reported they had no prior medical problems.

Metabolife's handling of adverse event reports exhibits callous indifference to the health of their consumers. Fourth chart shows careless handling of consumer complaints. Nearly 90 percent of the reports of adverse event reports submitted by Metabolife omit basic information, such as the age and gender of the consumer or the date of the incident. Nearly one-third of the reports of adverse events are handwritten with notes that are almost illegible. The recordkeeping is chaotic. Chart 5, I think, shows that.

This is the company receiving reports from their consumers about deadly symptoms, and look at the records that they are keeping on these. Here, we have a good example of a totally chaotic adverse event report. Looking at the record, you have no idea whether this is one caller or many callers, yet this person reported having a stroke. This is a very serious event, yet this is the level of care that Metabolife gave to noting that event, this from a company that claims their consumers' health is their No. 1 priority.

The next chart is another example. A 25-year-old reports having a stroke, yet Metabolife has no information on this report, just three handwritten lines. In over 99 percent of the significant adverse event reports, there is no mention of Metabolife requesting additional medical records needed for Metabolife to evaluate the role of its product in this adverse events.

FDA regulations require drug manufacturers to report adverse events including hospitalization, life-threatening adverse reactions, or death within 15 days of receipt. In no instance did Metabolife report adverse events involving hospitalization, adverse life-threatening adverse reactions, or death to FDA prior to its August 2002 submission. The Metabolife records contradict Metabolife's claims that it was unaware of consumer complaints of adverse health effects.

When we had our last hearing, we asked them how many adverse events had been reported to them and they only identified 78

adverse health effects. Now we all know better. They turned over thousands of records to the FDA and we have taken the time to go through them.

The next chart is a quote from Metabolife saying they did not have adverse event reports against an example of a report that they had received prior to their statement that they had none. On repeated occasions, Metabolife told Federal regulators it never received reports of adverse health effects from its consumers. In February 1999, for example, Metabolife informed the Food and Drug Administration, "Metabolife has never been made aware of any adverse health events by consumers of its products. Metabolife has never received a notice from a consumer that any serious adverse health event has occurred."

You have just seen them, charts with people who have reported strokes, and Metabolife said they were never reported. They never received such a report. Metabolife had received over 100 reports of significant adverse events before these statements were made, including reports of heart attacks, strokes, seizures, and psychosis that were received prior to the February 1999 statement to the FDA.

The case of a 25-year-old female stroke victim that I mentioned earlier was reported to Metabolife in 1998, and on this chart, here we have a consumer reporting that in September 1997, they suffered heart damage that their doctor says was caused by Metabolife. The record here is damning for Metabolife. They can try to skip around their own words and disavow the common meanings of an adverse event in the English language, but I think it is clear to any reasonable person that suffering a heart problem or a stroke and reporting it to Metabolife is clearly the reporting of an event that adversely affected the customer.

Finally, I want to point out one further item not mentioned in the report but I think it bears on Metabolife's real intentions to avoid reporting. In Texas, there is a law that requires Federal manufacturers to put the FDA MedWatch number on their products so that consumers suffering an illness that they believe may be related to the product can report it to the FDA. While Metabolife does comply with the law by putting the number on the bottle, they failed to identify what the number is for. They failed to identify it as FDA MedWatch.

The label reads, "TX:1–800–332–1088." Below this number is the phrase, "Health questions 800–490–5222." That number is Metabolife's own call center, the last one I read. So Metabolife has set up a system to divert people with health problems away from the FDA and to their own call center, where the adverse event report may sit for years and years and years without any action.

Actions speak louder than words, and Metabolife's own actions contradict their glossy PR statements.

I would now like to call the second panel for testimony this morning, if they would please come to the table. We have on this panel Lanny Davis, counsel, on behalf of David Brown, the President and CEO of Metabolife International, Incorporated, a company in the business of manufacturing dietary supplements; Dr. Howard Beales, III, Ph.D., Director of the Bureau of Consumer Protection at the Federal Trade Commission; Bill Jeffery, the National Coordi-

nator for the Centre for Science in the Public Interest at Carleton University in Ottawa, Ontario, Canada; Dr. Ron Davis, a member of the Board of Trustees at the American Medical Association based in Chicago, and if I am not mistaken, I saw Ron Davis a week or two ago in Chicago, is that correct?

Dr. RONALD DAVIS. Yes.

Senator DURBIN. Ron Davis is also, if I am not mistaken, a medical advisor to the Chicago Cubs. Did you not tell me that?

Dr. RONALD DAVIS. No, that is not me.

Senator DURBIN. Oh, I am sorry. Steve Adams, I think, came up to me at a restaurant in Chicago and said, "I am the medical advisor to the Chicago Cubs and you are right on on ephedra. This is dangerous." Thank you for being here, Ron.

Dr. Sid Wolfe, the Director of the Health Research Group at Public Citizen; and Dr. Frank Uryasz, the Director of the National Center for Drug-Free Sport in Kansas City, Missouri, for the National Collegiate Athletic Association.

Thank you all for coming, and I would like to note for the record I invited Robert Occhifinto of NVE Pharmaceuticals, the manufacturer of Yellow Jackets, to testify. We were apprised late last week he is on trial in New York and could not be here. Counsel for the company has advised my staff that answers to any questions should be sent in letter and they will try to respond.[1] I am disappointed that Mr. Occhifinto couldn't be here because I would like to have him explain to us and to the Riggins family and others about the product that he is selling.

It is customary to swear in the witnesses, so if you do not mind rising again. Do you solemnly swear the testimony you are about to give is the truth, the whole truth, and nothing but the truth, so help you, God?

Mr. LANNY DAVIS. I do.

Mr. BEALES. I do.

Mr. JEFFERY. I do.

Dr. RONALD DAVIS. I do.

Dr. WOLFE. I do.

Mr. URYASZ. I do.

Senator DURBIN. The record indicates that all witnesses answered in the affirmative.

I would like you all to try to make your oral statements in the neighborhood of 5 minutes and then I will ask some questions. Mr. Davis, would you please begin?

TESTIMONY OF LANNY J. DAVIS, ESQ.,[2] COUNSEL ON BEHALF OF DAVID W. BROWN,[3] PRESIDENT AND CHIEF EXECUTIVE OFFICER, METABOLIFE INTERNATIONAL, INC., SAN DIEGO, CALIFORNIA

Mr. LANNY DAVIS. Thank you, Senator, and thanks for giving me the opportunity on behalf of Metabolife to present perhaps some other perspectives.

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[1] Question and response from Ullman, Shapiro & Ullman, LLP, New York, NY, for Mr. Occhifinto appears in the Appendix on page 177.

[2] Questions and responses of Mr. Lanny Davis appears in the Appendix on page 166.

[3] The prepared statement of Mr. Brown submitted by Mr. Lanny Davis appears in the Appendix on page 59.

But let me start by expressing personal, as well as a message on behalf of Metabolife, to the Riggins family and to Mr. and Mrs. Riggins. We denounce and we condemn the abusive marketing practices of this company that resulted in the tragic death of this young man. We denounce companies, such as the company that is responsible for Yellow Jackets, who aim at marketing these products to young people, to athletes, who tempt them into abusive conduct and who hide the dangers of misuse of these products from young people.

And I am, unfortunately, with Metabolife associated with these characters and we want to do whatever we can do, as you will hear from my testimony, to clean the situation up in the industry and to work with you and the FDA. You will have our wholehearted support.

I would like to make three brief points, Senator Durbin, and I hope even though I am outnumbered at the table that you will give me an opportunity to speak once or twice again, if you think it is appropriate.

The first point I would like to make, Senator, is that our product is for weight control purposes and only marketed for weight control purposes and only marketed for adults. Our label says, consult a physician before you use our product for weight control. Whether you go to a gym or take SlimFast or take Metabolife, our label says consult a physician.

We also ask people to read our label carefully. We do not expect young people to read the fine print, but we ask adults who take our product under the supervision of a physician to read the label carefully. Dosage limitations are important. To those with preexisting medical conditions, such as heart disease or high blood pressure, we say, don't take Metabolife. We want an educated public to deal with the problem of obesity, which is the second biggest killer, next to cancer, in America. But we don't want people taking this product who are not supervised by a physician and who don't read our label carefully.

We are even willing to pay for a public education campaign, in light of some of these tragic results, to be sure that people under the age of 18 are banned from using our product. We would urge the Congress and State legislatures to require IDs and driver's licenses before anybody under the age of 18 is allowed to use the product. We do that for alcohol. Why not do it for ephedrine products?

Senator you have referred to the adverse event reports, and in retrospect, there is certainly a lot that we could have done differently over the years and I have no problem conceding to you that. But I would at least commend to you that when you use the word "cause," when you suggest causation, at least read the very authorities that you have cited to raise a question whether these anecdotal telephone calls constitute any evidence of anything.

The General Accounting Office would disagree with every word in Congressman Waxman's staff's document that suggests causation. In fact, the Food and Drug Administration in their adverse event reports was criticized by the GAO because of the unreliability of some of these telephone calls.

One of the many adverse event reports that is relied upon by my friends in the media and by my friends in the Congress when they criticize ephedra and one of the numbers that you have used was a 78-year-old woman who called the FDA and said Metabolife caused her to menstruate. That is one of the adverse event reports that is being relied on on that chart, at least the 1,400 number that your staff and others have relied on from the FDA, not on the ones that we gave to your Subcommittee, include that one. Another one of the 80 deaths that you often hear about is somebody who died in a car accident.

So all we are suggesting is, read the GAO report. The FDA on its website says you cannot rely on these AERs for causation.

You cited the *New England Journal of Medicine* study and the Mayo Clinic study. Both of those studies, Senator, are based upon the very same AERs that the GAO said are not to be relied on. They are not based upon clinical trials. They are based upon telephone call data that the GAO said is unreliable.

I suggest to you, respectfully, that when the *New England Journal of Medicine* was used by critics such as Dr. Wolfe in his Public Citizen petition as a basis for asking for a ban, read the letter from the authors of the *New England Journal of Medicine* report, Drs. Haller and Benowitz, in a letter to the editor, who said you cannot rely on our report as evidence of causation, the very same report that the Mayo Clinic and everyone is citing.

So to conclude, Senator, let me tell you what we are for and let me tell you what we at Metabolife would like to do. We applaud your concerns and we applaud what you are saying about the FDA. We have been asking the FDA to regulate this industry. We have asked the FDA to ban 18-year-olds and under. We have asked the FDA to set dosage limits based upon clinical trial results. We have asked the FDA to impose national standards for manufacturing practices.

And with respect to some of the unfortunate examples that have been cited to criticize Metabolife on our voluntary recordkeeping, unlike anyone else in the industry, we did this voluntarily. Nobody required us to keep these records. The system evolved over the years. We are not proud of some of those early years where we were very haphazard about the records we kept, but we certainly did include and we did voluntarily turn these over.

But we will say this to you, Senator, on and off the record—we will support legislation imposing a national mandatory call reporting system to the FDA, with a consistent questionnaire, with required follow-up so that we have a database, a national database that we can look at to achieve results. We also would certainly work with your Subcommittee on anything that constitutes a science-based regulation that would be aimed at adults who want to deal with the problems of weight control.

I would also like to just finally ask you, as a matter of fairness, Senator, I have known you for many years and you are one of the most fair people that I have ever known, at 8:15 p.m. last night, I received a fax of Congressman Waxman's staff report. We turned over these records to you and your staff almost 2 months ago. I understand and I certainly appreciate how hard your staff has been working, but to hand over a report at 8 p.m. at night and then

hand it out to the press in the morning, without my even having had a chance to read it and observe it, is just unfortunate, and I would at least appreciate your consideration to give us an opportunity, perhaps in another public setting with equal attention by my friends in the media, to give us an opportunity to respond to a report that we got in almost the middle of the night.

Thank you, sir.

Senator DURBIN. You went to bed early if 8:15 is the middle of the night.

Mr. LANNY DAVIS. Well, I actually was up for most of the night trying to read it, but I didn't have any help, so——

Senator DURBIN. Thank you. Mr. Beales.

TESTIMONY OF J. HOWARD BEALES, III, PH.D.,[1] DIRECTOR, BUREAU OF CONSUMER PROTECTION, FEDERAL TRADE COMMISSION

Mr. BEALES. Mr. Chairman, I am Howard Beales, Director of the Bureau of Consumer Protection, Federal Trade Commission. The Commission is pleased to have this opportunity to provide information concerning our efforts to ensure the truthfulness and accuracy of marketing for dietary supplements, including weight loss products and other supplements containing the herbal ingredient ephedra. Let me discuss the Commission's mission and our latest activities in the weight loss area, in particular. Please note that my oral remarks and the answers to questions represent my own views and do not necessarily represent the views of the Commission.

The mission of the Federal Trade Commission is to prevent unfair competition and to protect consumers from unfair or deceptive practices in the marketplace. As part of this mission, the Commission has a longstanding and active program to combat fraudulent and deceptive advertising claims about either the health benefits or the safety of dietary supplements.

As the Subcommittee is aware, the dietary supplement industry represents a substantial and growing segment of the consumer health care market. It encompasses a broad range of products, from vitamins and minerals to herbals and hormones.

There is no question that some of these products offer the potential for real health benefits to consumers. The scientific research on the associations between supplements and health is accumulating rapidly. Unfortunately, unfounded or exaggerated claims in the marketplace have also proliferated.

The FTC Act prohibits unfair or deceptive practices, including deceptive advertising claims made for dietary supplements. In addition, FTC law requires advertisers to have a reasonable basis for advertising claims before they are made. We filed more than 80 law enforcement actions over the past decade challenging false or unsubstantiated claims about the efficacy or safety of a wide range of dietary supplements.

Included in these actions are four cases challenging unqualified safety claims for supplements containing ephedra. These actions have included products marketed as alternatives to street drugs, such as Ecstasy, as well as body building supplements and energy

[1] The prepared statement of Mr. Beales appears in the Appendix on page 79.

supplements. We have additional non-public investigations pending that include both safety and efficacy claims for ephedra products.

Under the FTC Act, an advertiser is required to have competent and reliable scientific evidence supporting claims made in advertising before they are made. Thus, where advertising makes unqualified safety claims for ephedra products, we have challenged those claims as deceptive.

The orders that we have obtained in these cases both prohibit unsubstantiated safety claims and require a strong warning about safety risks in all future advertising and labeling by those companies. In addition, the order against Global World Media Corporation for its marketing of ephedra as a street drug alternative includes a prohibition against marketing in media targeted at young audiences.

Ephedra, of course, is frequently marketed as a weight loss product. We recently completed an analysis of weight loss product advertising. Our analysis found that 23 ads, or about 8 percent of the 300 ads we sampled, identified ephedra, ephedrine, or ma huang as an ingredient. Of these, 11 made safety claims, or 48 percent. Seven, or 30 percent, included a specific health warning about ephedra's potential adverse effects.

It is important to understand that these numbers almost certainly understate the prevalence of ephedra product advertising. Sixty percent of the sampled ads that made a safety claim didn't identify ingredients, so we are not sure whether they were ephedra products or not.

Finally, I would emphasize that in all of our dietary supplement cases and particularly in cases raising safety concerns, we work closely with and receive excellent support from the staff of the Food and Drug Administration. The FDA has both the expertise and the principal statutory authority to oversee the safety of dietary supplements. We view our activities on supplement safety as playing an important supporting role to FDA's more comprehensive efforts to ensure the safety of dietary supplements.

In conclusion, I would like to thank the Subcommittee for focusing attention on this important consumer health issue and for giving the FTC an opportunity to discuss its role. The Commission looks forward to working with the Subcommittee on initiatives concerning our dietary supplement program and our activities involving weight loss product advertising. Thank you.

Senator DURBIN. Thank you, Mr. Beales.

Mr. Jeffery, thank you for coming to this hearing from Canada. We made reference at an earlier hearing to action taken by the Canadian Government involving this product and I am glad that you are here today to tell us a little bit about that decision and about your views on this important health issue.

TESTIMONY OF BILL JEFFERY, L.LB.,[1] NATIONAL COORDINATOR, CENTRE FOR SCIENCE IN THE PUBLIC INTEREST (CSPI), CARLETON UNIVERSITY, OTTAWA, ONTARIO, CANADA

Mr. JEFFERY. Thank you, Senator Durbin. My name is Bill Jeffery. I am the National Coordinator for the Centre for Science and

[1] The prepared statement of Mr. Jeffery appears in the Appendix on page 91.

the Public Interest in Canada. CSPI is an independent health advocacy organization that is funded entirely by 125,000 subscribers to our Nutrition Action Healthletter in Canada. CSPI does not accept funding from industry or government.

I am pleased to have the opportunity today to address the issue of how ephedra and other dietary supplements, or what we call natural health products in Canada, are regulated. I was specifically asked to address seven questions and my written statement contains full answers to all of those and I would ask that it be incorporated into the public record.

Senator DURBIN. Without objection.

Mr. JEFFERY. I will summarize my responses here. Following two prior public advisories concerning health risks associated with ephedra and ephedrine, Health Canada determined that, on the basis of at least 60 adverse reaction reports and one death in Canada, and on the basis of similar international evidence, these products constituted a class one health risk for some vulnerable population groups. A class one health risk is defined by Health Canada as "a situation where there is a reasonable probability that the use of or exposure to the product will cause serious adverse health consequences or death."

Accordingly, Health Canada issued a voluntary recall of the offending products—I will describe what a voluntary recall is more later—on January 8, 2002. CSPI supports the recall because the small benefit of taking ephedra to lose weight, about one or two additional pounds per month for up to 4 months, is not worth the risk of stroke, cerebral hemorrhage, heart attack, and death. Experts may quibble over individual reports of adverse reactions, as Mr. Davis has on behalf of Metabolife, but it is beyond dispute that ephedra has triggered many serious complications and deaths in the United States and Canada.

At least nine organizations in Canada issued notices of Health Canada's voluntary recall on their websites, including the Canadian Medical Association and the Canadian Pharmacists Association. In addition, the Canadian Health Coalition and the British Columbia Medical Association publicly criticized Health Canada for not taking even stronger steps to prevent the sale of ephedra-containing products.

Currently, the Canadian Food and Drugs Act and regulations do not include a special regulatory category for herbal remedies. Accordingly, they are technically considered to be drugs and could be regulated as such by Health Canada. However, until forthcoming natural health product regulations are in place, Health Canada has decided only to take regulatory action against natural health products posing health risks or making claims about the health benefits in relation to 40 million diseases and health conditions specified in the act.

On December 22, 2001, the Federal Government proposed a set of regulations that, if approved, would establish a regulatory framework for issuing revokable licenses for natural health products and for production facilities and for setting standards for good manufacturing practices, speedy mandatory adverse reaction reporting, and labeling disclosures.

Currently, the Food and Drugs Act does not technically empower the Minister of Health to issue mandatory recalls for either drugs or natural health products. However, Health Canada's experience is that requests for recalls are almost universally respected, making it virtually unnecessary to resort to more rigorous enforcement powers authorized in the act, such as seizing products or obtaining injunctions against sale.

Health Canada also issued a voluntary recall and stop-sale directive for products containing the herb Kava on August 21 of this year after receiving reports of four non-fatal liver toxicity cases in Canada. Since November 1999, Health Canada has issued at least 11 other voluntary recalls involving 38 natural health products.

That is the essence of my submission, Mr. Chair. I would be happy to entertain any questions you may have.

Senator DURBIN. Thank you very much, Mr. Jeffery. Dr. Ronald Davis.

TESTIMONY OF RONALD M. DAVIS, M.D.,[1] BOARD OF TRUSTEES, AMERICAN MEDICAL ASSOCIATION, CHICAGO, ILLINOIS

Dr. RONALD DAVIS. Good morning, Senator Durbin. You mentioned the Chicago Cubs when you introduced me, so perhaps I should mention that I was born and raised in Chicago.

Senator DURBIN. Close enough.

Dr. RONALD DAVIS. I went to a lot of Chicago Cubs games when I was growing up, and despite their lack of success through the years, I do have a special place in my heart for the Chicago Cubs. So if they do need some sort of consultation, I would be glad to oblige.

Senator DURBIN. They need something, that is for sure. [Laughter.]

Dr. RONALD DAVIS. Consultation about health matters, not how to play baseball.

I am Ron Davis. I am a member of the American Medical Association Board of Trustees and I am pleased to be able to testify here today on behalf of the AMA, and I would like to thank you and the Subcommittee for holding this hearing. As a preventive medicine physician, I work at the Henry Ford Health System in Detroit as Director of the Center for Health Promotion and Disease Prevention.

The physician members of the AMA are very concerned about the quality, safety, and efficacy of dietary supplements. The AMA believes that the Dietary Supplement Health and Education Act of 1994, or DSHEA, fails to provide for adequate Food and Drug Administration oversight of dietary supplements. We have urged Congress to amend DSHEA to require that dietary supplements be regulated the same way as are prescription and over-the-counter medications.

To respond to the six questions the Subcommittee has asked us to answer, it may take a little bit longer than the 5 minutes allotted, but I will be as concise as I can.

Question one was, why has the AMA asked FDA to remove dietary supplement products containing ephedrine alkaloids from the

[1] The prepared statement of Dr. Ronald Davis appears in the Appendix on page 96

U.S. market? The AMA has encouraged the FDA to remove dietary supplement products containing ephedrine alkaloids from the U.S. market. We believe the FDA has sufficient cause to take action under Section 402 of the Federal Food, Drug, and Cosmetic Act. Under the FDCA, these products should be deemed adulterated. They pose an unreasonable risk of illness or injury under conditions of recommended use in the labeling.

The AMA's position is based on several considerations. The FDA has received more than 1,000 voluntarily submitted adverse event reports, or AERs, for ephedrine alkaloids. Some of these reports, as has been mentioned already, describe death or serious injury in young, presumably healthy adults. There are many, many more actual adverse events. In fact, one company alone recently admitted to having received more than 14,000 AERs for dietary supplements containing ephedrine alkaloids since 1995.

In 1996, after reviewing over 800 AERs, the majority of members of the FDA's own Food Advisory Committee reported that, "based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements." The Advisory Committee recommended that the FDA remove ephedrine alkaloids from the market. In 2000, FDA-commissioned outside experts reviewed another 140 AERs and reached similar conclusions. Unfortunately, the FDA has not taken the advice of these experts.

It is difficult, we acknowledge, to prove cause-and-effect relationships based on voluntary AERs. However, we believe the FDA must consider whether manufacturers' claims of benefits outweigh the products' risks. Purported uses for ephedrine-containing dietary supplements include weight loss, energy enhancement, athletic performance improvement, body building, and euphoria. The AMA strongly believes that these uses are of questionable benefit, with little, if any, clinical data to support efficacy. With the high number of AERs and the extremely questionable uses of ephedrine alkaloids, the benefit-risk ratio of these products is unacceptable.

The second question was, do ephedrine alkaloids pose the same risk for hemorrhagic stroke as phenylpropanolamine, or PPA. Ephedrine alkaloids and PPA are sympathomimetic amines. Since there have been no controlled clinical trials comparing ephedrine alkaloids to PPA, we do not know if ephedrine alkaloids pose the same increased risk for hemorrhagic stroke as PPA. While the AMA supports controlled clinical studies on the serious adverse events related to ephedrine alkaloids, these studies are not necessary to remove ephedrine alkaloids from the market immediately.

Question three, should herbal ephedra be available by prescription only in the United States? The AMA strongly supports the removal of dietary supplements containing ephedrine alkaloids from the U.S. market. Whether ephedrine alkaloids that are regulated as drugs should be available in the United States is an open question. The manufacturer would have to submit safety and efficacy evidence to the FDA for pre-market review. If the evidence shows a benefit-risk ratio that justifies approval for marketing, then the products could be marketed as drugs.

Question four, what are the dangers of taking ephedra-containing products without medical supervision? Because of ephedra's effects on the cardiovascular and central nervous systems, it may

cause arrhythmias or disturbances in the heart rhythm, heart attacks, sudden death, stroke, and seizures. These can occur in both healthy individuals and in those with risk factors for these conditions. The risk of adverse events may increase when ephedrine is combined with other stimulants, such as caffeine. The risk may also increase depending on the content of ephedrine alkaloids, which varies considerably from product to product and within different lots of the same product.

Question five, explain the difference between a patient taking a prescription drug for obesity under a physician's supervision and a consumer taking an ephedra product for obesity without any screening for medical conditions that would suggest that the consumer was a poor candidate. Obesity is a significant public health problem in the United States. It should be categorized as a disease. Appropriate treatment of obese patients requires a comprehensive approach involving diet and nutrition, regular physical activity, and behavior change. Emphasis should be placed on long-term weight management rather than short-term extreme weight reduction. Physicians play an important role in promoting preventive measures and encouraging positive lifestyles, as well as identifying and treating obesity-related diseases.

The AMA concurs with the National Institutes of Health drug treatment recommendations for adult obesity and believes that prescription anti-obesity drugs, such as Orlistat and Sibutramine, may be given as an adjunct to nutrition therapy and exercise. Ephedra-containing dietary supplements should not be used for weight loss.

And finally, question six, has the AMA taken initiatives to ensure that, in discussing weight loss with their patients, physicians explain the possible dangers of ephedra-containing products? The AMA is currently developing a primer for physicians on assessment and management of adult obesity for release next year. We would be pleased to share this primer with Members of the Subcommittee at that time.

In conclusion, because dietary supplements are classified as foods under Federal law, they are assumed to be safe and are subject to limited regulatory oversight. However, dietary supplements containing ephedrine alkaloids have significant risks which may be serious or fatal and far outweigh any benefit from the product. These significant side effects, regardless how rare they may be, are unacceptable in the absence of proven benefits. For these reasons, we urge the FDA to initiate proceedings to remove dietary supplements containing ephedrine alkaloids from the U.S. market.

Thank you again for the opportunity to testify before the Subcommittee and we would be happy to answer questions.

Senator DURBIN. Thank you very much. Dr. Wolfe.

TESTIMONY OF SIDNEY M. WOLFE, M.D.,[1] DIRECTOR, PUBLIC CITIZEN HEALTH RESEARCH GROUP, WASHINGTON, DC

Dr. WOLFE. Again, thank you and your staff for all the work that went into this hearing. There has been a notable absence in the last 12 years of constructive oversight such as this hearing, I think, is attempting and succeeding in doing, of the FDA. One of the rea-

[1] The prepared statement of Dr. Wolfe appears in the Appendix on page 104.

sons, I think, that the FDA has run amok so much in the last 12 years has been not enough oversight.

This hearing is especially essential because of the extreme reckless negligence exhibited by dietary supplement companies who continue to sell ephedra-containing products and because of the industry enfeebled Department of Health and Human Services, including the FDA, that has thus far allowed the companies to get away with continuing to manufacture and push these deadly drugs.

The next minute or two of information, I confirmed yesterday after I turned in the testimony, so it is something that is not in the version you have, but I think it is probably as important as anything I have to say. It has to do with the fact that the U.S. military, in a way, is putting HHS and FDA to shame.

I have learned from a fairly high-ranking military health professional that from 1997 through 2001, there were 30 deaths among active duty personnel in the Armed Forces—Army, Air Force, Navy, and Marines—in people who were using ephedra alkaloids. All were between the ages of their early 20's and early 40's. All had been in good health prior to their deaths. There was no other explanation for their deaths.

Since then, there have been three additional deaths associated with the use of ephedra products in the Army alone, so we are talking about 33 deaths in about 1.4 million active duty personnel. To be sure, the reporting is much better in the Army, Navy, Air Force, and Marines than it is in the general population, but if this is any glimpse as to what the problem nationally would be if we had better reporting, we are talking about hundreds, if not over 1,000 deaths that may well have occurred in people using these products.

The history of medicine precedes the more recent science of epidemiology. Most of the associations and causations that we know between products, environmental, occupational exposures, and disease are from case reports, case reports looked at very carefully in which you could not find any other explanation.

Partly as a result of these 33 deaths and other serious non-fatal adverse events in military personnel associated with ephedrine, in July of this year, memos were sent to all Army and Air Force military exchanges and commissaries worldwide stating that by the end of August, just a month-plus ago, all ephedra-containing products should be removed from the shelves in these military posts for 6 months until the results of the HHS ephedra review are released.

One of the most interesting statements I found in conjunction with this ban in the military bases—the Marines had banned it last year on their bases—was a statement by an Army physician, Dr. DeKonning, and it really speaks again to the whole existence of these products anywhere. He is talking about them on military bases. "The sale of ephedra-containing products by these military facilities is seen by our soldiers as an affirmation that their use is safe and acceptable," and I think that generally the country believes that the existence of these on the market, in supermarkets, gas stations, anywhere else, is an affirmation by the government that the use is safe and acceptable, and it is not.

I will now again, as Dr. Davis did, get to some of the questions that you would ask. One, you asked for the basis for our September 5, 2001, petition with Dr. Ray Woosley of the University of Arizona

to ban the manufacture and sale of all ephedra-containing supplements. Two questions need to be asked before answering this. One is, do drugs which are related to epinephrine, or adrenaline, such as ephedrine, phenylpropanolamine, amphetamines, and similar drugs, cause an increase in blood pressure, constriction of blood vessels, an increase in heart rate, or an increase in cardiac arrhythmias? The answer is unequivocally yes, and this has been known and published about for decades.

The second question is, is there evidence that these drugs can cause stroke and heart attacks in people because of causing an increase in blood pressure, constriction of blood vessels, heart rate, or cardiac arrhythmias? Again, the answer is unequivocally yes for all these drugs.

We discovered, in a document that I don't believe your Subcommittee staff had seen before, a memo from the head of drugs at the FDA, from 2½ years ago, on a request from the Food Safety Division of FDA to do a thorough look at all these case reports, and Dr. Woodcock, in concluding what her own epidemiologists had found in reviewing these reports, stated that "at least 108 of the reports"—these were clinically significant cardiovascular and central nervous system reports—"that were analyzed provide very strong evidence in support of a causal relationship between ephedra alkaloid-containing dietary supplements and the adverse events, particularly in light of the known pharmacodynamic effects of these alkaloids, such as increased pulse, blood pressure, and arrhythmias."

Again, the question that you asked Dr. Davis, is there some incongruity between what happened with phenylpropanolamine and what has not happened with ephedra? There clearly is. This is a dangerous *deja vu* to where we were 10 or 12 years ago with phenylpropanolamine. There were far fewer reports of death and these serious problems with phenylpropanolamine than we now have with ephedra, and yet the FDA bought into an industry-hatched scheme to do a study and thereby delay taking this off the market.

With PPA, dozens or more lives were lost and many people permanently damaged between the time FDA clearly should have acted and when they finally got the drug off the market. To repeat this fatal mistake with ephedra is to fail to learn the lessons of history.

Another question had to do with how do you look at the benefit-risk analysis for these products. Thirty years ago—more than 30 years ago—an FDA physician was removed from his post because he said obesity is a chronic disease and there is no evidence that these drugs affect the course of the disease over the long term. He used this logic to reject the FDA approval then of a drug called Pondimin, or fenfluramine, the same kind of chemical that was in the noted notorious fen/phen and which has now been taken off the market. I think the statement is still true. In the long term, as Dr. Davis said, the policy has to focus entirely, I believe, not just largely, on diet and exercise kinds of approaches as opposed to drugs.

You also asked us about our own petition earlier this year to ban Meridia Sibutramine, which again has some properties that are amphetamine-like. At the time that we filed our petition in March, there were 19 reported cardiovascular deaths in people using the

drug, far fewer than with ephedra. The fact that there is no evidence of long-term benefit with either Meridia or ephedra means that the benefit-risk ratio is completely unfavorable, or as Dr. Davis said, unacceptable.

Senator DURBIN. Dr. Wolfe, if you could wrap up, please.

Dr. WOLFE. I can. I just have one or two more points to make and I will.

You already have gone over the issue of the Mayo Clinic study, where most of the people were taking the recommended dose, sort of disproving the idea that you have to have high doses.

The final thing I want to say is this is not really a question of scientific or medical evidence. It is a question of politics and the extraordinarily dangerous political cowardice of the FDA and Secretary Thompson in the face of massive lobbying by ephedra makers, such as Metabolife, in Washington. Is the FDA still part of the Public Health Service or is it a drug sales promoting adjunct to the pharmaceutical and dietary supplements industries? De facto drug pushers include those who refuse to use their legal authority to remove a well-documented, unequivocal hazard to the public from the market.

There is no doubt that these products will be banned in the United States. The question is not whether, but when. Delaying tactics, such as the RAND review that the government asked for, are costing lives as the day of reckoning for ephedra is thereby delayed. There are few issues that the AMA and Public Citizen agree upon. Tobacco and ephedra, which Ron and I have worked on together for a long time, are two of these. The FDA has been rejecting the opinions of its own consultants and staff, such as Dr. Woodcock, on the dangers of ephedra alkaloids.

Senator DURBIN. Thank you very much, Dr. Wolfe.

Mr. Uryasz, thank you for being here.

TESTIMONY OF FRANK D. URYASZ,[1] PRESIDENT, NATIONAL CENTER FOR DRUG FREE SPORT, INC., KANSAS CITY, MISSOURI ON BEHALF OF THE NATIONAL COLLEGIATE ATHLETIC ASSOCIATION

Mr. URYASZ. Thank you, Senator Durbin, for allowing the NCAA to inform you of the Association's work in the area of deterring the use of ephedrine. I am Frank Uryasz. I am President of the National Center for Drug Free Sport, a private company in Kansas City, Missouri. We provide drug testing and drug education programs for athletic organizations and our clients include the National Football League, the NCAA, and many colleges and universities.

Drug Free Sport administers the drug testing program for the NCAA, and accordingly, the NCAA asked me here to represent it today. Joining with me are Mary Wilfert and Abe Frank from the NCAA national and Washington offices. I am representing about 1,200 colleges and universities, 360,000 student athletes who are competing at these schools.

One of the principles that guides the NCAA is that the NCAA and its member institutions have a responsibility to protect the

[1] The prepared statement of Mr. Uryasz appears in the Appendix on page 112.

health and safety of the student athletes, and the NCAA commits significant resources to meet that principle. Those resources include a full standing committee of medical experts, the NCAA Committee on Competitive Safeguards and Medical Aspects of Sport. They issue sports medicine guidelines on educating athletes about dietary supplements. The NCAA employs health and safety staff in their national office in Indianapolis. They have national drug testing programs, educational seminars, and they conduct national research regarding drug and supplement use among athletes.

Since 1985, the NCAA has conducted a national drug and supplement use survey. It has been replicated every 4 years. Over 21,000 student athletes participated in the most recent survey in 2001.

Prior to the 1997 replication, the NCAA Competitive Safeguards Committee, their medical committee, was monitoring the growing use of dietary supplements, and accordingly, on the 1997 study included questions for the athletes about their supplement use and specifically ephedrine use. Three-point-five percent of the athletes surveyed reported that they had used ephedrine within the last year, and the highest use was in the sport of wrestling, at 10.4 percent. Fifty-one percent of users said they used ephedrine primarily to improve their athletic performance, and many used right before or during practice or competition.

The NCAA was concerned that the use of ephedrine was being so closely linked to athletic performance and the committee recommended in July 1997 that ephedrine be added to the list of banned drugs. The NCAA has two national drug testing programs, and accordingly, has a list of banned substances and ephedrine has been included in that list since 1997.

The NCAA instituted drug testing at its championships in 1986 and any NCAA athlete competing at those championships and bowl games is subject to the strict drug testing rules of those events. Approximately 1,500 athletes are tested at those events each year and any who test positive, including those who test positive for ephedrine, lose their collegiate eligibility for at least 1 year.

The second drug testing program was implemented by the NCAA in August 1990. It applies to about 10,000 student athletes each year and its focus was to deter the use of anabolic steroids.

In 2001, the NCAA replicated its national drug use study and found that the use of ephedrine had actually increased and that 24 percent of the athletes said they used it to improve performance, 22 percent used it as an appetite suppressant, 22 percent for health reasons, and 20 percent said to improve their appearance. Due in large part to the 2001 survey findings, the NCAA decided to add ephedrine to its year-round drug testing program, and accordingly, about 10,000 athletes will be tested for ephedrine this year.

The NCAA's prevention efforts are significant. The NCAA funds the Dietary Supplement Resource Exchange Center. The REC provides a toll-free number and website for student athletes to get reliable information about the effects of supplement use. Any reports of health effects are automatically reported to the FDA MedWatch program. The NCAA has educational programs. They publish posters deterring the use of supplements, including ephedrine, sponsor educational conferences, has a national speakers' bureau of experts to talk about supplement use, and has issued a number of reports

in *The NCAA News* and even sent an advisory to all NCAA schools in the summer of 2001 about supplements.

All of the NCAA schools have agreed to legislation not to distribute supplements that fall outside specific restricted categories and ephedrine is prohibited under any circumstances.

Ephedrine, as you know, is contained in a multitude of sports supplements, energy bars, power drinks, and supplement pills. It is fair to say those of us who educate young people on the dangers of supplement use feel like the proverbial lone voice in the wilderness of supplement marketing.

The NCAA is committed to reducing the demand side of the dietary supplement problem in sports. The organization wishes to make known today that it is willing to partner in any national effort that will enhance student athlete health and safety. Thank you.

Senator DURBIN. Thank you, Mr. Uryasz.

I thank the entire panel. I would like to ask a few questions. There, incidentally, is going to be testimony this afternoon from Dr. Lester Crawford from the FDA.

Let us have this as a starting point. Most people are surprised when I talk to them about this issue because they think, mistakenly believe, that when it comes to a lot of these products, the Federal Government is in on this, that we are doing things to protect consumers. They mistakenly assume that when it comes to products like dietary supplements with ephedra or ephedrine, that the Federal Government, the Food and Drug Administration have watched it carefully all the way through the process.

Now, when it comes to drugs, and I defer to Dr. Davis or anyone else here who would like to step in if I miss a point here, the Food and Drug Administration has a responsibility to determine that drugs are safe and effective, two very basic but important standards, and to establish their safety and efficacy, they go through clinical trials for years to make certain that they are safe and effective, and once having been approved by the FDA, they are carefully monitored as to the way that they are manufactured so that it is done in a healthy and safe way, and then carefully monitored in terms of the impact they have on the general population once released for sale.

This applies to over-the-counter drugs as well as pharmaceutical drugs, and as a result, adverse event reports become very important, because if you start learning that thalidomide is causing genetic problems and birth defects in babies, this otherwise what appeared to be safe drug is going to be studied more carefully or removed from the market, which happened.

Mr. LANNY DAVIS. Senator, may I try to answer that one?

Senator DURBIN. When I get finished, you may.

Mr. LANNY DAVIS. I am sorry. I thought you were done.

Senator DURBIN. And then, of course, the question is whether or not these adverse event reports are accumulated and reviewed by the government to see if something is happening about a drug that they otherwise thought might have been safe, and if that conclusion is reached, it might be removed from the market, as thalidomide was removed.

In the situation here when we are dealing with dietary supplements, the only prohibition is from making any explicit health claim related to treating a disease. Good manufacturing practices as to how Yellow Jackets or Metabolife are being made are in the process of being established. We passed this law 7 or 8 years ago, 1994, if I am not mistaken, but it really is a totally different situation.

The government's involvement in the approval, review, and monitoring of this particular product is virtually zero, negligible. The government's approval of Yellow Jackets, same thing, not involved in it, really. If they don't make a health claim that brings in the FTC, they do what they want to do, and that is what leads us to this hearing today and what leads me, Mr. Davis, to ask you, did Metabolife mislead the Food and Drug Administration in 1999 when it informed them, "Metabolife has never been made aware of any adverse health events by consumers of its products"?

Mr. LANNY DAVIS. Senator, I will answer that question, and then, if you would give me an opportunity, I would like to also address your earlier comments and some of my prior colleagues' comments.

First of all, it is my understanding this matter is under investigation by the authorities. The sentence expressed by the individual that you have mentioned expressed the understanding that adverse event reports meant some link to a causation analysis. That is what I have been told was the understanding, and beyond that, since this is under investigation, it is just not possible for me to comment any further.

Senator I know I am outnumbered and I know there is a very powerful set of colleagues and persuasive colleagues sitting next to me, but——

Senator DURBIN. Mr. Davis, I might add that if Mr. Occhifinto of NVE had accepted our invitation, you would not be so outnumbered.

Mr. LANNY DAVIS. But we are here and we are here to respond and, gratefully, to be allowed to respond to your concerns and the concerns expressed here. I would like to raise, in response to your inquiry about the Food and Drug Administration and what it does or does not do, that it does regulate over-the-counter drugs. I would like to make four points here.

First, it does regulate over-the-counter drugs. There is an over-the-counter drug called Primatene Mist. Primatene Mist has 150 milligrams of ephedra in it. It is used for therapeutic purposes as a bronchodilator. There is no restriction on having a cup of coffee with Primatene Mist and we, in fact, on Metabolife's label restrict use to less than 150 milligrams for an entire——

Senator DURBIN. I am going to stop you right there, because let me ask you this question. Metabolife 356, does it contain both ephedra and caffeine?

Mr. LANNY DAVIS. Correct.

Senator DURBIN. Is there any over-the-counter drug approved by the Food and Drug Administration which contains both ephedrine and caffeine?

Mr. LANNY DAVIS. I am not aware of any, but I would ask——

Senator DURBIN. As a matter of fact, before you go further, it has been banned since 1983. So this product could not be sold over-the-counter under FDA approval. So you may talk about Primatene Mist, but there was a decision made 20 years ago that the combination that you have in this drug is not safe enough to be sold to Americans, and yet you continue to sell it as Metabolife 356. Please proceed.

Mr. LANNY DAVIS. Senator, I think you——

Dr. WOLFE. Can I respond, because he has made a very misleading statement.

Senator DURBIN. I will let him finish.

Mr. LANNY DAVIS. Senator, I think in fairness, I do not think it is fair if I do not have a chance to finish my point.

Senator DURBIN. You are being given plenty of time, Mr. Davis.

Mr. LANNY DAVIS. All right, thank you, and I know that you will allow me, and I am sure that there are responses to everything I have to say.

Regarding your comment on an over-the-counter drug, you are absolutely correct, but there is nothing that the FDA has ever imposed as a restriction on taking caffeine along with Primatene Mist, is my only point, and if there were a danger, one would think that the FDA would provide that.

The three facts that I want to bring to your attention, fact No. 1, Senator, there are 30 studies over the last 15 years, many of them involving clinical trials of human beings taking ephedra-caffeine combinations similar to Metabolife and placebo, double-blind, peer reviewed, published studies, one recently by Harvard and Columbia University that has been published, and many others that have shown that when dosage limitations similar to our label and other preexisting medical conditions are avoided, that we tell people not to take our product if you have the preexisting medical conditions listed on our label, clinical trials involving human beings, there has never been a single instance where the placebo group showed more significantly fewer or less severe adverse events than the group using Metabolife and caffeine. That is over 15 years and 30 such studies.

Now, I ask you to ask any colleague here, I asked Dr. Davis, my counterpart with the great last name, on national television, can you cite a single clinical trial involving human beings, supervised by a scientist and published anywhere, that has shown a significant difference in adverse events between the placebo group and the——

Senator DURBIN. I think you have been given ample opportunity. Before I ask Dr. Davis to testify, pause and reflect a moment what the industry is saying. The government has to prove that there is something wrong with the product. This is exactly the opposite of what happens with the Food and Drug Administration in terms of drugs sold by prescription and over-the-counter in America. When it comes to these drugs, the companies have to prove first that they are safe instead of the government proving that they are unsafe, and that really is why we have created, I guess why some voted to create this exception here.

Dr. Davis, if you would like to respond.

Dr. RONALD DAVIS. Senator Durbin, you have really struck at the crux of the issue just a moment ago, an issue that we believe is central to this whole debate, and that is, should dietary supplements be exempted from the normal regulatory procedures that are outlined in law for over-the-counter and prescription medications. An exemption written into the DSHEA law in 1994, we think was a mistake. As a result, as you pointed out, prescription and over-the-counter medications have to be shown pre-market to be safe and effective, underscoring the word "pre-market." That is No. 1.

No. 2, the burden of proof for prescription and over-the-counter medications is on the manufacturer to establish safety and efficacy based on valid scientific studies. But for dietary supplements, instead, companies are allowed to manufacture and market these products and you get to a point where thousands or millions of people are using them without any of that pre-market proof, and then the burden of proof, as you said, is on the FDA to show harm after thousands or millions of people have already been using them and after serious injury and deaths have occurred.

Beyond that, with over-the-counter and prescription medications, the adverse events are required to be shared from the manufacturers to the FDA, whereas in the case of dietary supplements, that requirement is not there in the law. And so as a result, we have had the difficulty that you have talked about with regard to Metabolife. So we believe that the 1994 legislation should be changed so that dietary supplements face the same sort of regulatory oversight as over-the-counter and prescription medications.

Senator DURBIN. Mr. Jeffery, when you listen as a Canadian, interested in public health and following your country's debate here, when you listen to this debate which I have just outlined, where in 1994 we created a new category, dietary supplements and vitamins and minerals and the like, and said that we are going to treat them differently in terms of the government's responsibility, can you give us any kind of perspective from your point of view as to how Canada has viewed this and how they reached the decision to take the very same products that FDA will not address off the market?

Mr. JEFFERY. Yes. It seems clear that both the Food and Drug Administration and Health Canada have had access to the same body of scientific evidence. In fact, the death rate attributable to ephedra and ephedrine-containing products in the United States, if anything, is ten times as high per capita in the United States as in Canada. If Dr. Wolfe's estimates are borne out, it may be 100 times as high.

Senator DURBIN. Wait a minute. Let me make sure it is clear on the record. You are saying that the adverse events, serious adverse events in the United States are tenfold larger than what you experienced in Canada——

Mr. JEFFERY. Right.

Senator DURBIN [continuing]. And yet you have had a recall of dietary supplements containing ephedrine.

Mr. JEFFERY. To an outside observer, the difference in approach of the two countries is really only explainable by two things. Either the DSHEA Act has completely undermined the Food and Drug Administration's authority to protect American citizens, or the Food

and Drug Administration believes that American lives are cheaper than Canadian lives.

Mr. LANNY DAVIS. May I respond, Senator?

Senator DURBIN. Who is asking to respond? Do you want another chance?

Mr. LANNY DAVIS. Please, very briefly. First of all, Senator, we believe we should have to produce positive evidence of safety, not negative evidence of danger. I understand your point about DSHEA. We believe there should be affirmative evidence of safety for our product to be used just for weight control. Senator, let me read you the sentence——

Senator DURBIN. I want to make sure I understand it. You are saying that you believe your industry should have a responsibility to affirmatively prove the safety of your product?

Mr. LANNY DAVIS. Correct, not——

Senator DURBIN. Before it is marketed?

Mr. LANNY DAVIS. Not by statute. That is the difference between DSHEA.

Senator DURBIN. Then how would you enforce that?

Mr. LANNY DAVIS. Well, we are doing it—let me read to you one recent study, and if there is any doubt about the validity of this, we can go back 15 years. This is the Harvard and Columbia study that says—it was a 6-month study—"compared with placebo, the tested product produced no adverse events and minimal side effects."

Second, regarding my colleague from Canada, who I greatly respect, Senator, the background rates—this is a fact—the background rates for heart attack, seizure, and stroke in the general population of the United States, according to Dr. Kimmel of the University of Pennsylvania, is no different than the rates of those occurrences by people taking ephedra-based products for weight control. Let me repeat that. This is not tobacco. This is not a statistical aberration that Dr. Wolfe argued from in his Public Citizen petition, the Mayo Clinic using the same AER data, everybody using AER data that even my colleague, Dr. Davis, agrees is not reliable. Fact, the background rate of these occurrences in the general population are the same percentages, according to Dr. Kimmel, as you find among Metabolife users.

I am only using that to suggest that if we are going to ban a product, rather than what I agree with you on is strict and tough regulation, then I would suggest we need science, not junk science, as a basis for public policy, based on fact, not innuendo.

Senator DURBIN. Mr. Davis, you are a very skillful lawyer and I respect you for that.

Mr. LANNY DAVIS. Thank you.

Senator DURBIN. But I would just tell you that there were several things here that argue against your case, and I think very convincingly. The reed that you are hanging on to is Boozer's study. Are you aware of the author of that study, Carol Boozer, in a deposition for the case of *Harvey Levin v. Twin Labs,* stated that her study was not designed to study safety, in spite of its title? In speaking about the small sample size, Dr. Boozer said, "The number of subjects was based on the outcome of weight loss and we did not conduct a power analysis to determine the number of subjects

for other parameters." She discounted the use of that study, which you are hanging on to with all of your strength as the basis for defending your industry.

Let me also tell you that I am troubled when we have to parse words here and think about causation. Dr. Davis and the AMA have been involved in tobacco wars, on my side, thank goodness, for many years and we have fought this battle. Does tobacco cause cancer? Does it cause heart disease? You can remember all of the "scientists"——

Mr. LANNY DAVIS. Yes.

Senator DURBIN [continuing]. Who came out to show that, no connection whatsoever. We played that game for 40 years in America.

Let me just tell you, I cannot understand how Metabolife could be collecting all these adverse event reports, scribbling them on little pages, and ignoring them and really misrepresenting to the Food and Drug Administration whether you had even received them because you were not sure they were caused by your product. Those people found your company. They called your company. They believed they were caused, and in some cases, they had doctors to back them up.

So to argue here today that you are now going to be reformers in the industry, you are the ones who are going to step forward, but don't do it with law, let us take care of ourselves——

Mr. LANNY DAVIS. No——

Senator DURBIN. Excuse me, because I do not think you have a good track record.

Mr. LANNY DAVIS. Please let me respond to correct that last statement. First of all, we want a Federal regulation by the FDA. We agree with the AMA and others at this table, the FDA won't regulate us the way we want to get rid of some of the bad apples, like Yellow Jackets. We want a Federal requirement for national call reporting so these anecdotal reports that you have criticized don't happen again.

Finally, let me also remind you that I am not just citing Boozer-Daley, which is a peer reviewed, published study, an out-of-context quote, I must say. I am quoting 30 studies, Senator, 30 over 15 years, all of them showing no difference between placebos and control groups or other studies. The only evidence my colleagues are citing are anecdotal data.

Let me give you anecdotal data. Aspirin, in 1 year, 16,000 calls were made to the American Association of Poison Control Centers in Atlanta, 16,000 in 1 year. Of those, 5,900 were described by the National Center as adverse event reports.

Senator DURBIN. Mr. Davis——

Mr. LANNY DAVIS. Acetaminophen, Senator——

Senator DURBIN. Mr. Davis, you have been given plenty of chances.

Mr. LANNY DAVIS. I just wanted to point out acetaminophen.

Senator DURBIN. I would like to chair the hearing for a while, if you don't mind. Let me just add——

Mr. LANNY DAVIS. OK. Thank you for letting me speak.

Senator DURBIN. You are entitled to speak, but let me tell you what. Anecdotal evidence includes Sean Riggins. Anecdotal evi-

dence includes the experience at the NCAA. Anecdotal evidence includes the people who died in Canada leading them to make a decision to ban your product. But it was a scientific conclusion that when you put all that evidence together, the product that you are selling is more likely to harm people than to help them.

Mr. LANNY DAVIS. Not if it is used according to our label, Senator. We believe that it should not be used——

Senator DURBIN. Mr. Davis, please.

Mr. LANNY DAVIS. OK.

Senator DURBIN. According to your label, you are selling a product which has been prohibited over the counter in the United States for almost 20 years.

Dr. Wolfe, you wanted to say something earlier.

Dr. WOLFE. Just a couple things. In many of his misleading, if not false statements, Mr. Davis either is ignorant, which I don't think he is, or he is being a little mischievous, if not malicious.

You cite an example of Primatene, an over-the-counter asthma drug that does not contain caffeine. You put on the record that the ones that are in combination with caffeine have been gone for 19 years. The FDA proposed 7 years ago to ban all over-the-counter products with just ephedrine alone. That is in process. The last time I looked at the *Federal Register,* it was supposed to be completed and finalized by the end of this year, and I checked yesterday with the FDA. That is still completely on target.

So, again, the point you have made, Senator, is there appears to be a double standard based on the same kind of evidence. If anything, the evidence for this product working for asthma is far better, even though there are better products now instead of it, than for these other mainly ridiculous uses. So the FDA is taking that off the market with the legal authority it has for over-the-counter drugs.

We believe that the legal authority, although weaker, for dietary supplements says that if it is used as directed and causes an unreasonable risk of harm, it can come off the market. So despite all of the disabling aspects of the dietary supplement law, FDA has the authority, they know they have the authority, and they will use the authority. I mean, it is almost pitiful to listen to Mr. Davis sort of frantically trying to save his clients.

The studies he cites mainly were not designed to look at safety. There is actually a newer study by Drs. Benowitz and Haller, whose study was published in the *New England Journal of Medicine* a couple years ago. There is a newer one showing a big increase in blood pressure in people using these kinds of products.

So I think the evidence scientifically is completely in one direction. There has rarely been a drug taken off the market based on a "scientific epidemiological study." It is case reports and more case reports, or as the pejorative description is, there are just anecdotes. There are deaths in military people. There are deaths in others, in Sean, and where you have no other explanation but the product, and that is enough scientifically to take things off the market.

Senator DURBIN. Dr. Davis.

Dr. RONALD DAVIS. Senator, I would just like to make a couple of comments in response to the points that have been made in this discussion. First of all, Mr. Davis referred to a national TV pro-

gram that we were on recently. That was the "Weekend Today" show, and he did not mention a challenge that I posed to him, and that is that his company join with the AMA to go to Congress to ask Congress to amend the DSHEA law to put dietary supplements under the same regulatory authority as over-the-counter and prescription medications. He declined that challenge on television and his argument was that dietary supplements are "natural" products.

I think it is important for people to realize that the whole history of pharmaceutical development includes many products that have come from plants or botanicals. Digitalis, a potent heart medication, is a well-known example. Vinca alkaloids, which comprise chemotherapeutic agents for treating cancer, these are derived from botanicals, as well.

I also want to give you a specific example of where anecdotal reports were very informative and influential in public health policy in this country just very recently. A new vaccine was developed and was put into the marketplace for children, the rotavirus vaccine to prevent serious diarrheal illnesses in children. Shortly after that vaccine was introduced in the United States and began to be used nationally, we had reports of intussusception, which is a serious intestinal condition where intestinal blockage can occur and even death.

After anecdotal or individual reports of intussusception came in for children who had recently received the rotavirus vaccine, the CDC said, this is a red flag. We are concerned. We urge everybody to stop using this vaccine, and in the meantime, we are going to conduct, as quickly as possible, a large study to see whether this association is real. They quickly contracted with HMOs across the country, including very large ones like Kaiser, and collected information on, I believe, several hundred thousand kids who received this vaccine. Maybe it was even a million or more. My own institution, the Henry Ford Health System, participated in this study. In a matter of several months, they determined that these anecdotal reports of intussusception were borne out by a large valid study.

Now, the point here is that this product was taken off the market, was kept off the market to protect people until valid science could be done with an appropriate sample size, hundreds of thousands, at least. By comparison, the Boozer study which you brought up had a sample size of 83 people taking these dietary supplements, these ephedra herbal products, 83. If you think for a minute, what if 1 out of 500 people who used this product died because of the product? I am sure everyone would say that is an absolutely unacceptable risk, 1 out of 500 dying. Yet, if that was the case, and we do not know whether it is or not, but if that was the case, how could you detect that with a sample size of 83?

Senator DURBIN. Let me ask you, and I want to take this to a point which I want to make sure is clear in this hearing. We have talked about dietary supplements with ephedra and what the responsibility of the government should be. Even Mr. Davis on behalf of the industry is conceding that we need to stiffen the requirements in terms of the production and marketing of this product because of the danger.

But where do we draw the line here? The big debate on DSHEA in 1994, which flooded Capitol Hill with letters, was over whether

or not the Federal Government was going to require people to get prescriptions for their daily vitamins. I would not support that. I do not know that Members of Congress would. But where do we draw that line, then?

When we talk about vitamins and minerals and ordinary herbs that people may decide, if I want to take a garlic pill in the morning because I think it has some therapeutic value to me personally, it has not been proven, I do not believe, that that has any danger associated with it, I really should not have to get a prescription for it. Where is the reasonable place to draw that line?

We do not want to treat everything like a prescription drug or an over-the-counter drug, but we surely have a situation here where dietary supplements with ephedra are now creating so much havoc in terms of public health that the AMA and Canada and the NCAA and others have stepped forward in saying, if the FDA will not move, we will. Where do we draw that line?

Dr. RONALD DAVIS. Well, that is a good question. The quick answer that I would give is that there has to be a way to give some kind of expedited approval to products that have clearly been shown to be safe. The Food and Drug Administration has a list of products called GRAS, Generally Recognized As Safe, which pertains to food additives. There ought to be a way to have a similar category for dietary supplements which are known to be safe, even when used in excess. That way, we would not hold up things that clearly would not pose a serious risk to the population.

Dr. WOLFE. I think that for the vitamins and minerals, which I think the ban of which or the rendering by prescription, a very misleading kind of campaign by the industry, caused all this outpouring and caused the Hatch-Harkin law to pass, we have lots of information on safety and effectiveness and proper doses of vitamins and minerals, so I think those are easy ones. I think the other ones really should be treated like drugs. They are drugs. If they were not pharmacologically active, then their promotion would be entirely a fraud. We know they are pharmacologically active. They are drugs.

I think the DSHEA should be repealed, and there are Generally Recognized As Safe food additives as well as over-the-counter drugs. Vitamins and minerals would clearly fall into this category, and I do not think it is as much a problem as the industry has tried to inflame the public it is. I mean, this law is certainly one of the major, if not the major step backward in the history of the FDA, whose legal enhancement has been in the direction of more safety, more efficacy, starting with the safety law in 1938, the efficacy law in 1962, the device law in 1976. This is a major step backwards. It needs to be either so significantly amended that you won't recognize it or entirely repealed.

Senator DURBIN. Mr. Jeffery.

Mr. JEFFERY. Yes. I can send a copy to the Subcommittee of the Canadian Government's proposed definition of natural health products. It has a functional component and included and excluded lists of substances which may be of use to the Subcommittee.

But I would just like to comment on a reference that was made to the naturalness of dietary supplements. I think it goes without saying that food is natural. Our Canadian Food Inspection Agency

put ephedra and Kava on a list of 15 herbs that it refers to as toxic and they are considered inappropriate to be used in foods. So I am not sure that Mr. Davis can have any resort to the naturalness of the products. There is no need to be caught up in that distinction.

Senator DURBIN. Mr. Beales, in terms of the FTC, has DSHEA created some problems from your side? Has it created new challenges in terms of advertising of these products?

Mr. BEALES. Well, from our perspective, DSHEA didn't change anything because our approach to advertising has always been based on, do you have a reasonable basis for the claims that you are making, and so that approach was something that is very comfortable to the FTC and something that we have always pursued. What it has done is, I think, some of what was intended, was to increase the market for these products, and that has increased the volume of claims that we see, certainly.

I think, by and large, the distinction that DSHEA makes between health claims and structure function claims is one that mostly works. There are some supplements like ephedra-containing supplements that raise special issues. But most of the things that are supplements don't have the kinds of adverse events associated with them that ephedra does.

Senator DURBIN. Mr. Uryasz, if I might ask you, you have had a ban, an NCAA ban on these products by athletes and yet you have seen an increased usage by most surveys here. What does it tell you? What do we need to do to get the message out to people who are obviously conscious of their bodies and their health but are making the wrong decision, and more seem to be making it despite good warnings?

Mr. URYASZ. In the field of drug and supplement use prevention in sport, we have to look at the supply side and the demand side. An organization like the NCAA has done a tremendous job, I believe, on the demand side of the problem. Nothing has been done on the supply side. These athletes have easy, easy access to these substances. The advertising is targeted directly at both our male and female student athletes.

You mentioned earlier, where do you draw the line? I would suggest you do not draw the line at 17 or 18 years old. That does not provide any relief for the 360,000 student athletes that I represent who, for most of them, are 18 to 22 years old that right now can legally buy ephedrine.

Senator DURBIN. I might add, Ann Marie has brought this up a couple of times, but this is the website from these folks, NVE, who couldn't make it today, for their Yellow Jackets, and if you read this, it is kind of a challenge to young people. Warning, Yellow Jackets are not recommended for novices with limited experience in the use of herbal energizers and fat burners. It was specially, [misspelled] formulated for seasoned consumers of such products. It does not strike me that that is an age warning. It is kind of a challenge. Are you a big boy? Can you do this? Or are you a novice?

Mr. URYASZ. Let me just say, the magazine that I held up, one of the supplements we get a number of questions on, Hydroxycut, which is another one that stacks the ephedrine and caffeine, this is a six-page advertisement for this supplement, but there is no mention of any of the warnings that are on the label.

Mr. LANNY DAVIS. Senator, may I surprise you by agreeing with most of what I have heard?

Senator DURBIN. Sure.

Mr. LANNY DAVIS. I do not want everybody to be upset with me, some may not want me to agree with them on this, but I certainly agree with the gentleman from the NCAA that it is not just under-18-year-olds. We do not think this should be marketed for athletes or athletic enhancement or any of the things that these kids are using, 18 or older or not, for popping pills. I said earlier, we only think you should use it for weight control under the supervision of a doctor and that there are medical conditions that absolutely should not allow you to use them, as we say on our label.

But let me at least address this one final point to you, Senator. We are only asking for a rifle shot focus in your inquiry, as well as a broad brush. We are only asking you to look at ephedrine-based products. I agree with the gentleman from Canada and Dr. Beales. This is a unique and possibly separate issue when you are talking about ephedra. We do not disagree with you on that. That is why we are asking for an FDA regulation aimed just at ephedra, because it is a different product. That is why we are asking for a national call reporting system, mandated across the country, just for ephedra-based products and no other products.

We are not insensitive to the Riggins tragedies and to the tragedies of other young people and athletes that have misused this product for purposes we do not support, and if there is any way to do a rifle shot rather than throwing the whole barrel out and to at least give some credit for whatever mistakes we have made, which I concede to you, Senator, we are not perfect, that we wanted—tried to be constructive. This is not just public relations. This is sincere.

Senator DURBIN. Mr. Davis, I am going to quibble or quarrel with your use of the word "misused the product." Time and again, we find people who have used the product as recommended are killing themselves with it, and you are finding that there is virtually no policing in terms of the sale of these products to children, who could not be expected to read all of this malarkey behind the label before they decide to pop a Yellow Jacket.

I want to make sure I understand you. Are you saying, then, that you would support changes in the law or new Federal regulation which would require medical supervision before people take Metabolife 356, to determine whether or not it is medically appropriate for them to use this product?

Mr. LANNY DAVIS. I am not in a position to say a new Federal law, but I can tell you that I have just said exactly that this product should not be taken for weight control without a doctor's supervision. We agree with Dr. Davis on that. I am not in a position to say we would support a specific law until I see it. But we would certainly work with you on the regulation, on the reporting system, and on that kind of child I.D. requirement, so that we have driver's license required before you buy this product.

There is a lot we agree on. There may be some who disagree on it, Senator, but at least we are here and we are trying to find common areas that we do agree with you on.

Senator DURBIN. Thank you very much.

I am going to close at this point. Dr. Wolfe, did you want to——

Dr. WOLFE. Just quickly. The only way that you can guarantee that a product is used with doctor's supervision is to switch it to prescription status. Does Mr. Davis agree with that?

Senator DURBIN. I was going to raise the same point, but once you have a doctor involved in it, it sounds like a prescription.

Thank you very much. We are going to recess this hearing until 2:30, when Dr. Crawford will be here. To this panel, thank you for your contribution.

[Lunch recess.]

AFTERNOON SESSION

[2:30 p.m.]

Senator DURBIN. Good afternoon. The continuation of this morning's hearing before the Senate Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia, focusing on "Ephedra: Who is Protecting American Consumers," will resume.

I am happy to welcome to this gathering Dr. Crawford from the Food and Drug Administration and hope that you will be able to give us your agency's perspective on that, and I would like to begin with the customary swearing in of witnesses.

Do you solemnly swear the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you, God?

Dr. CRAWFORD. I do.

Senator DURBIN. Thank you. Let the record reflect that the witness has answered in the affirmative. Dr. Crawford, please feel free to make your statement.

TESTIMONY OF LESTER M. CRAWFORD, D.V.M., PH.D.,[1] ACTING COMMISSIONER, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. CRAWFORD. Thank you, Mr. Chairman. I appreciate this opportunity to speak to the Subcommittee about the dietary supplement ephedra. Before I go into detail about this particular dietary supplement, let me briefly describe the foundation for FDA's regulatory and enforcement actions on all dietary supplements.

In 1994, the Dietary Supplement and Health Education Act created a unique regulatory framework for dietary supplements in the United States. This framework is primarily a post-market program, as is the case for foods in general. Should safety problems arise after marketing, the adulteration provisions of the statute come into play.

Under DSHEA, a dietary supplement is adulterated if, among other things, it or any of its ingredients presents a significant or unreasonable risk of illness or injury when used as directed on the label, or under normal conditions of use if there are no directions. FDA bears the burden of proof to show that a product or ingredient presents such a risk. In addition, the Secretary of Health and Human Services has the authority to declare that a dietary supple-

[1] The prepared statement of Dr. Crawford appears in the Appendix on page 116.

ment or dietary ingredient poses an imminent hazard to public health or safety.

DSHEA specifically grants FDA the authority to develop good manufacturing practices. There is broad public support for dietary supplements good manufacturing practices. Such regulations are critical to assuring quality, purity, and consistency in dietary supplement products. FDA has made the publication of a GMP proposed rule a high priority and we are in the final stages of that process. I am pleased to announce that last Friday, the proposed GMP rule was forwarded to OMB for a 90-day review.

As my testimony makes clear, we are looking forward to receiving the comprehensive review of the existing science on ephedrine alkaloids, particularly those found in dietary supplements. This review is being conducted by the RAND Corporation, which has targeted the end of the year to complete this effort. The results of the RAND review will help FDA's scientists develop future regulatory actions on dietary supplements containing ephedrine alkaloids. While we await the completion of the RAND review, this does not in any way preclude FDA in taking additional enforcement actions.

Last June, the administration announced that FDA is aggressively pursuing the illegal marketing of non-herbal synthetic ephedrine alkaloid products. Warning letters were sent to firms that were unlawfully selling non-herbal ephedrine alkaloid-containing products over the Internet. These products violate the law because they are not legally dietary supplements. They are unapproved drugs.

FDA has also warned other companies for illegally promoting its illegal ephedra product as an alternative to street drugs. Our latest action involved Yellow Jackets.

Mr. Chairman, thank you for calling to Secretary Thompson's attention the death of the 16-year-old boy who ingested the product Yellow Jackets in your letter of October 2, 2002. I referred the matter to our enforcement personnel, who identified a distributor in the Netherlands who is making claims that are illegal under U.S. law. The website indicates that the product is intended to be used as an alternative to illicit street drugs. It is, therefore, being illicitly marketed.

I know this comes as little comfort to the boy's family, who have suffered such a tragic loss, but yesterday, FDA issued a cyber letter to the foreign distributor and we alerted consumers that these products present health risk. We are working closely with law enforcement officials in the Netherlands and the U.S. Customs Service to block entry of Yellow Jackets into this country by placing this product on import alert.

In addition to our prior efforts on synthetic ephedrine alkaloid enforcement, FDA continues to assess additional products in the marketplace, and if circumstances warrant it, we will take further enforcement against products that contain synthetic ephedrine alkaloids.

Secretary Thompson has expressed concern about the safety of ephedra, and I share that view. The Secretary has requested that FDA evaluate as quickly as possible mandatory warning labels that can be justified by sound science. These labels would properly alert the public regarding the potential risk associated with consuming

dietary supplements containing ephedrine alkaloids. We will incorporate warning labels into our regulatory enforcement efforts at the agency.

I appreciate this opportunity to testify and I also would point out that today, we have announced the finalization of proposed rulemaking on dietary supplement good manufacturing practices. Secretary Thompson has issued a statement saying that, "We continue to take steps available to us to protect the public and implement our strong commitment to protecting people in this country from the dangers of unlawfully marketed drug products."

And then, finally, we are continuing our efforts to prevent marketers from advertising ephedra products as alternatives to street drugs and we have taken some actions so far, and including one today against a company in New Jersey.

I am pleased to be here. Thank you, sir, and I am happy to answer your questions.

Senator DURBIN. Thank you, Dr. Crawford.

Let us go right into your last statement here, because I was concerned. I wrote a letter to the Secretary on October 2 about Yellow Jackets after I heard about Sean Riggins, whose photo is here, who died near my hometown after taking this product, and I made a point in that letter—I am sure you have seen it—of noting that this product, this Yellow Jacket here, is a product made by NVE Pharmaceuticals of New Jersey. Now, the action which you have taken apparently relates to a firm in the Netherlands, but then you just closed by saying, we took action against a New Jersey firm. So have you taken action against NVE Pharmaceuticals?

Dr. CRAWFORD. Yes. We are in their plant as we speak today and taking action to inspect the plant for a variety of concerns, their manufacturing and also their marketing. We have been denied entry into the plant and we are taking action to get access to the plant legally through the courts, and that should be consummated before the day is over.

Your letter alerted us to this situation, as I indicated earlier, and we did trace the source, the original source, to the Netherlands. But then we were able to determine that the product was actually manufactured in the United States, in New Jersey, in the plant that I mentioned. Therefore, that led us to investigate them.

Senator DURBIN. Well, let me ask you, what is likely to occur if the court follows the lead of the FDA in reference to NVE Pharmaceuticals? What actions, if you could be more explicit, will be taken against this company?

Dr. CRAWFORD. We don't know what we will find when we gain access to the plant. That will be done immediately. What we are seeking is a warrant, as you would know, to allow us entry, even though they have denied that to us. Once we get into the plant, we will examine records and anything else we can find and then take the appropriate steps.

Senator DURBIN. So are you suggesting or testifying that you are going to stop all Yellow Jackets, or just those that are marketed as alternatives to street drugs?

Dr. CRAWFORD. We are certainly going to take action as strongly as we can against those that are marketed as street drugs. We have evaluated the product and the composition of it seems to me

to be inconsistent with the use for which it is intended, so it is my belief that the investigation will probably lead us to take stronger action—strong action against all Yellow Jackets and all Yellow Jacket manufacturers and we will try to interdict them from commerce.

This particular product, as you know, has a warning on it about consumption by persons under 18 years of age. That is not a legal warning. It is actually a warning that is a sales policy and, therefore, is not enforceable. And the composition of the products all seem to be cardio-stimulatory and I am very doubtful as to whether or not there is a legitimate use for the product.

Senator DURBIN. Let me ask you this. Are you going to stop with Yellow Jackets? Are there other ephedrine-based products that you are going to——

Dr. CRAWFORD. There is another product called——

Senator DURBIN Supplements containing ephedra that you are going to pursue?

Dr. CRAWFORD. There is another product called Black Beauty, and——

Senator DURBIN. I am familiar with it.

Dr. CRAWFORD. In the past, apparently, these seem to be interchangeable. The only difference is a stippling coloration as opposed to a yellow-type coloration. So I think it is about the same thing and we intend to take action against those, also.

Senator DURBIN. And is that basically, again, because there is a suggestion that it is an alternative to a street drug? Is that the basis for your action?

Dr. CRAWFORD. It is easier for us to go after them if they are an alternative to a street drug because the claims that they make clearly indicate that you can use this rather than some street drug, and also, they indicate that they use the same terminology and language as you would use for street drugs, like rushes and highs and so forth.

However, both these products seem to be so cardio-stimulatory and also have so much ephedrine in them that I would suspect that we are probably going to conclude that they can't be safely marketed.

Senator DURBIN. Both of these products, I called to the attention of Secretary Thompson in my letter of October 2, and I am glad you are taking action on them, but this begs the question, do Members of the Senate and Congress now have to write to the Secretary with individual names of individual products, the products that are associated with victims, in order to get action by the FDA against these companies?

Dr. CRAWFORD. We have been maintaining surveillance of these kind of products for some time. As a matter of fact, we established our street drug policy about a year ago. So our enforcement actions have been continuing apace. I don't want to minimize the letter that you sent to us, but it is our job to find out about these kind of things and we are redoubling our efforts in that regard.

Senator DURBIN. Let me ask you some more general questions that might get us back to this same issue. Do you believe that nutrition supplements containing ephedra are safe and effective?

Dr. CRAWFORD. Well, I think there are a couple of general statements I would make about that and then get as specific as you would like for me to be. It seems to me that as I review all of the indications and claims for use and also the dosages and even the dosage forms that they are marketed for inappropriate things. Weight loss and energy are not the kind of things that are attributed to these kinds of drugs.

As you know, they have been used as drugs for many years as an alternative for ephedrine, as something that is fairly close to amphetamine. The amphetamines were disallowed as diet intervention products some years ago and the whole class has. The ephedrine and its various congeners are used for legitimate medical purposes, sometimes under the supervision of a physician, sometimes over the counter. But they are not used legitimately for weight loss and energy and those kind of things, for the most part. They do have some usages in medicine, but I can't quite understand why they are marketed for that.

So I would say it is a drug that, were it a prescription drug or were it under the supervision of a physician, would have legitimate uses. I am having trouble with these particular uses.

Senator DURBIN. This really goes to the heart of our concern, and to the heart of the problem. Under DSHEA, do you have the authority to remove a nutrition supplement with ephedra from the market if you believe it is being marketed for use that can't be proven, for example, weight loss or energy builder?

Dr. CRAWFORD. The Dietary Supplement Health Education Act, as you know, places the burden of proof upon the FDA. Many other national and international entities that have interdicted the use of these products for this particular purpose have not had to establish the proof. We have had to do that.

I was on the Food Advisory Committee of the FDA in the middle-1990's when this first came up and although I have not been at the agency but about 10 months, I believe the agency has been working steadfastly to develop that case.

The answer to your question is that it has not really been tested to this point. I think the burden of proof has led us down a long and torturous path and is something that we were unaccustomed to at FDA.

Senator DURBIN. And the point that was made this morning, when it comes to prescription drugs and over-the-counter drugs, the burden of proof is on the manufacturer as to the safety and efficacy. Long clinical trials, scientific evidence presented to the FDA leading to market approval, then the drug comes to market and it is closely monitored by adverse event reports to see if there are any problems with it, and the FDA is continuing to watch and see if it is safe, and if it is effective.

When it comes to these drugs, naturally occurring drugs, if you want, the dietary supplements, exactly the opposite is true. These companies, unless you can bring them in under an alternative street drug provision in the law—just take Metabolife, for example, which by its name would not signal that you could bring it in as an alternative street drug, these companies can continue to market unless and until, as I understand it, the FDA can prove that they are not safe, and as you said, that is a long and winding road, of

proving causality between adverse event reports and the danger that might be associated with the drug. Is that a fair summation?

Dr. CRAWFORD. That is correct. Yes.

Senator DURBIN. Let me draw you, then, to the next question, on safety, because this really, as far as I am concerned, gets to the heart of the issue. It has been a decision by the Food and Drug Administration for 19 or 20 years now that the combination of caffeine and ephedrine or caffeine and ephedra will be prohibited in over-the-counter drugs. Do you know why that decision was reached or the basis for that decision?

Dr. CRAWFORD. As I understand it, you are talking about the drug side, on the over-the-counter products?

Senator DURBIN. Yes, that is right.

Dr. CRAWFORD. As I understand it, the reason it was reached is sort of two-fold. The safety of the two, since they are both stimulatory to the heart and also have central nervous system stimulation, is deemed to be not particularly indicated. In the era of specific pharmacology, what the agency has tried to do following the passage of the Kefauver-Harris amendments in the early 1960's is to insist upon a specific drug for a specific purpose and get away from what we call galenical preparations, where you had multiple drugs competing with each other. There was not seen to be any pharmacological reason to have these two together. If you wanted more stimulation, then perhaps you could alter the dose of one or the other. And also, caffeine sort of operates with flash-like suddenness and then it is gone, so it is hard to have the two in combination.

Then the second reason was is that there was concern about the safety, for sure.

Senator DURBIN. Which draws me, then, to this obvious conclusion. The FDA has banned ephedrine-caffeine over-the-counter drug combinations since 1983 or 1984. The FDA has banned PPA, a metabolite of ephedrine, over-the-counter drugs since 2001. The FDA is moving forward with banning ephedrine over-the-counter drugs, which was proposed in 1995. But when you put that combination in what is called a nutritional supplement or a diet supplement, the same combination, ephedra and caffeine, they are legal, though the 1997 proposed rule might have banned them. An herbal ephedrine is legal, as well.

Now, when it comes to the safety of people like Sean Riggins and the safety of the American public, how is it served by the Food and Drug Administration saying, when it comes to drugs, don't get near this combination. It is dangerous. But when it comes to nutrition supplements, like Metabolife, we have no role, no voice.

Dr. CRAWFORD. I have two responses to that. When I was on this Food Advisory Committee, I believe as early as 1994 but probably no later than 1995, we were presented the assignment to look into ephedra in combination and also separately because the agency was concerned about it. I think they were concerned because of the obvious fact that these products are not just herbals, if you will. They have pharmacologically active substances.

In fact, at about that time when the law was passed and we began marketing some of these, I think there was the feeling that maybe little harm would be done with most of the herbal remedies

that were on the market because they might not be particularly active, but actually, the opposite has turned out to be the case. Even products like St. John's wort have pharmacological activity that was, for the most part, unexpected.

With ephedra in combination with caffeine, it certainly has the same kinds of activity at certain levels as the former drug combination, so there is great concern about it, and it is an incongruity and I grant you that.

Senator DURBIN. Well, let us go to the heart of it. If, in fact, we have already established pharmacologically that this combination can be dangerous, and if, in fact, we have evidence of the danger in terms of the adverse event reports to Metabolife, the deaths of young people like Sean Riggins, and actions that have been taken by others, is it not true that the Secretary has the power to suspend the sales of this product in the United States today, even under existing law?

Dr. CRAWFORD. I think the route that was taken was to establish the causality, in other words, to do the proof. If you look back into the records on the restriction of the use of the drug, ephedra with caffeine, essentially, what happened under that law, the Federal Food, Drug, and Cosmetic Act, was that FDA asked the sponsors, that is, the manufacturers of the product, to give them safety and effectiveness data, and when that was not forthcoming or it was not forthcoming in a form that was useful, the agency simply said, we are not satisfied and, therefore, the product has to come off the market.

With these particular products, the determination was made that we have to, in effect, become the sponsor of the product. That is, we have to go through the safety tests and the evaluation, and that was begun, as I mentioned, as early as 1995 and reached a crescendo in 1997. It still hasn't been done.

Your point about what the Secretary's options are, is he can, based on the evidence, declare these products basically unsafe for use as indicated, and then, in effect, they are converted to a drug. He also has the option under the law, as I understand it, to declare an imminent hazard, and then that begs the question of whether or not they can be marketed while the imminent hazard procedure is proceeding or whether you leave them on the market until it is concluded. Imminent hazard is a long, torturous process, also, and it has not been attempted since the middle-1980's, when it failed for the fourth time, with another drug category—prior to the law.

Senator DURBIN. My first letter to Secretary Thompson after the initial hearing was August 6, and I called on him to do exactly that, to make an immediate determination that these dietary supplements containing ephedra posed a hazard to the health of American consumers, and I went on to say, it is within your authority to take this step and suspend the sales of the supplements until their safety is clearly and scientifically established.

You have, I think, just said in your testimony that the Secretary has the power to do that, and my question to you is, were you asked by the Secretary any time after this letter was sent to him to sit down and give him advice as to whether he should suspend the sales of this product?

Dr. CRAWFORD. Yes. I was asked to tell him what the status was, and so I reported on the RAND report. He was eager for this to be concluded. We also about that time received a CD–ROM from one of the manufacturers of ephedra which contained some adverse event reports, large numbers of them. So my recommendation to the Secretary was, let us try to build this case, finish building this case as rapidly as possible. The RAND study, as I mentioned in my testimony, is scheduled to be completed early next year. And also to wrap up all the details of these previous studies and make a hard and fast recommendation to him.

In typical Secretary Thompson fashion, he wants that done sooner than later and we are on target to try to get it done early next year.

Senator DURBIN. Dr. Crawford, I don't want to be harsh with the Secretary or yourself in terms of this issue, but I do have to point out something. When I sent this letter on August 6 and asked for the suspension of sales of this product, Sean Riggins was still alive. Nothing has happened. I shouldn't say nothing has happened. The sales have not been suspended. Obviously, there has been a lot of discussion within your agency. And now, I believe you are saying that by the end of November, some decision will be made, is that correct?

Dr. CRAWFORD. A recommendation will be made by me to the Secretary.

Senator DURBIN. I would say to you that I can't understand why we have suspended or held up this decision. It would seem to me that with the accumulated evidence of deaths and serious illnesses resulting from this product, that the wise, prudent, good faith effort would require suspension first, before we go into a long and elaborate study. I mean, it isn't as if we are talking about something that has a salutary effect on people. This is a killer for people who are unsuspecting, particularly children. Why wouldn't we take that off the market even sooner? Why wasn't it done sooner?

Dr. CRAWFORD. You mean like back in the 1990's?

Senator DURBIN. Well, I can certainly go that far back, but let us start with August 6. Why isn't it——

Dr. CRAWFORD. Well, the——

Senator DURBIN. Here we have the accumulated evidence. Canada, which I think we acknowledge to be a country not dissimilar to the United States in many ways, in their standards of public health, they made the decision calling for a voluntary recall of this product. In January of this year, the American Medical Association wrote to the Secretary. We know that over 20 States have established regulations because of their fears.

We now have evidence that 30 or more members of the U.S. military have died from the use of this product and it has been suspended on military posts across the world. We know the action has been taken by sports organizations to keep it out of the hands of athletes because of the fear. You had the adverse event reports presented to you, I believe in August or September of this year from Metabolife, which gave ample evidence that even though they stated otherwise in 1999 to the FDA, they were receiving serious adverse event reports for 5 years.

All of this seems to be building a body of evidence, which, if I were in your position or Secretary Thompson's, I would say the clear and prudent thing to do to protect Americans, take this product off the shelf. We can debate later on the proper dosage and whether we need a doctor involved and sales to minors. But at this point in time, this is a killer and our obligation is to the American public. What am I missing in my logic here?

Dr. CRAWFORD. Well, I don't think you are missing anything. I am not disagreeing with you, either. The situation is that the burden of proof is on us and we have to make the case, and once we take the action, we have to be able to sustain it.

As I mentioned, the agency has gone down the path of following DSHEA and trying to build a case to take either this unsafe product action, which would lead to declaring it a drug, in effect, or the imminent hazard action, or, based on what the evidence reveals—we have to be guided by the science and——

Senator DURBIN. May I address the science for a moment?

Dr. CRAWFORD. Yes, sure.

Senator DURBIN. Are you familiar with Dr. Janet Woodcock of the Food and Drug Administration?

Dr. CRAWFORD. Yes.

Senator DURBIN. Have you read her memo to Joseph Levitt of March 28, 2000, relating to these products?

Dr. CRAWFORD. Yes.

Senator DURBIN. When we are talking about the science and the proof, Dr. Woodcock wrote to Mr. Levitt, the Director of the Center for Food Safety and Nutrition, on these dietary supplements containing ephedrine alkaloid, and I will just read a sentence or two here. "At least 108 reports that this office analyzed provide very strong evidence in support of a causal relationship between these supplements and the adverse events, particularly in light of the known pharmacodynamic effects of ephedrine alkaloids."

So within the Food and Drug Administration, over a year and a half ago, there was evidence from one of your doctors on staff that we have a problem here with this product. I wrote on August 6 and what you have said to me is, we need more study. We need more evidence.

Dr. CRAWFORD. No, we need to complete this study that they commissioned about that time. Now, what happened, Dr. Woodcock is obviously very highly respected. As a matter of fact, she is Director of the Center for Drug Evaluation and Research. What was done with her letter was that HHS in 2000 convened an expert panel of scientists to review her finding. Her finding essentially was that there was causality between ephedra use and serious disease events.

The conclusions of that panel was, in effect, an overturning of Dr. Woodcock's conclusion, and they called for more evidence-based research and analysis and that was what was done. Her recommendation was made in good faith. That was her professional opinion. When it was refereed by this expert panel, they concluded otherwise.

Senator DURBIN. So you are saying that there was a panel that came to a different conclusion about the linkage——

Dr. CRAWFORD. Yes.

Senator DURBIN [continuing]. And this panel, does it have a name or is it internal to the FDA——

Dr. CRAWFORD. It was a group of people that were appointed by the Department of Health and Human Services and they were internal. They were from NIH, the FDA, and other agencies within HHS.

Senator DURBIN. Well, are you in doubt as you sit here today about the danger of this product?

Dr. CRAWFORD. I am not in doubt about the fact that it can be dangerous. I am also not in doubt about concerns about the use to which it is being put in this form, as I mentioned earlier, for weight loss and energy and these kind of things. Until I make a recommendation to the Secretary, though, I can't make any definitive comment.

Senator DURBIN. Right. Understood. Let me ask you about this RAND study. Tell me a little bit about it. Who is involved in the RAND study and how many people who are reviewers in the RAND study have connections to the industries that they are reviewing?

Dr. CRAWFORD. The RAND Corporation is in charge of the RAND study and they are, in effect, contractors to the FDA, but they must meet the same ethical standards as we ourselves do, our expert panels do. So we have vetted the people involved in the study for any conflicts of interest and I am informed that they are within the reasonable bounds that we have to operate under.

What they are doing is an analysis of all the published work on ephedrine and have been at it for some time and are expected, as I mentioned, to complete it very soon now.

Senator DURBIN. And you feel that this study by RAND is going to be objective and scientifically credible?

Dr. CRAWFORD. Yes, I do.

Senator DURBIN. All right. Let me ask you, as well, if you could tell me, you probably heard the testimony, or perhaps someone told you about the testimony today from Lanny Davis, an attorney representing Metabolife. He was calling for some dramatic changes in the way this product is going to be sold in America. He didn't want a law——

Dr. CRAWFORD. I am sorry, Senator——

Senator DURBIN. This is Metabolife.

Dr. CRAWFORD. OK.

Senator DURBIN. Metabolife. He didn't want, if I state it correctly, if I remember it correctly, he didn't take the bait when I said, do you want to change the law? He thought that might be a little excessive. But he did suggest that there be changes by regulation, FDA regulation, to establish a variety of things that he called for—limitations on sales to minors, good manufacturing practices that are going to be followed, medical supervision and the like, perhaps even some information developed on proper dosages, I suppose.

Do you have the authority to do that? Could you follow his suggestion and establish those standards for a specific product, namely dietary supplements containing ephedra?

Dr. CRAWFORD. I would have to evaluate his recommendations and perhaps study them a wee bit, but I can respond to these items that you mention.

On the GMPs, the 1994 law did call for good manufacturing practices that would be effected through regulation and it also stipulated that they had to be based on food GMPs, that these products would be treated as foods rather than as drugs, and that regulation, for a variety of reasons, was never published. We have completed that, and as I mentioned earlier, it is at the Office of Management and Budget for their customary 90-day review. We expect to hear from them, therefore, by the end of the year. As soon as we get the report back from OMB, we will publish it.

Ultimately, when it becomes final, this will provide guidance to the industry on how they are to manufacture these products and that will be an improvement. More importantly, we can use adherence to the GMPs, or lack of adherence, as a means of enforcing some of these things. As a matter of fact, it is the main enforcement tool that is present in DSHEA, so we need it out.

Senator DURBIN. And am I correct in saying that the law that was enacted in 1994 and this effort to establish GMP for these products, we are now some 8 years into this conversation?

Dr. CRAWFORD. Yes.

Senator DURBIN. And how soon do you think we may have a standard for products that are being sold every day across America?

Dr. CRAWFORD. Well, what I am committed to do is to get it out as soon as possible. We have to have this review, as I mentioned, and then we will be ready to publish it unless something is found to be defective about it. We have already had it vetted by the Office of General Counsel and the Office of Chief Counsel and I believe that it is an intact and usable document. So I expect the best.

When we publish it, it will be published as a proposed rule and we are going to take comments on it. About the earliest any of these get put into a final rule is 6 to 9 months and it can take as long as 4 years.

Senator DURBIN. Four years from now?

Dr. CRAWFORD. Yes. That is in the extreme, and——

Senator DURBIN. It seems like we are in an extreme situation——

Dr. CRAWFORD. Yes.

Senator DURBIN [continuing]. If we are 8 years into it and still may have 4 years to go.

Dr. CRAWFORD. I agree. I don't disagree with that at all. They need to be out because they are guidance to the legitimate industry as well as a means of taking enforcement actions against the industry that is not operating correctly.

Senator DURBIN. Dr. Crawford, are we meeting our obligation to the American public when we can't establish a standard for good manufacturing processes in 8 years, maybe 12?

Dr. CRAWFORD. I can't—please accept my situation here. I just came in February and this was proceeding at that point.

Senator DURBIN. Welcome to the Federal Government.

Dr. CRAWFORD. Thank you, sir. [Laughter.]

It seems a little longer than February. In fact, you and I have met together at least twice before, not on this subject, but on other subjects. I think there are good and sufficient reasons they weren't able to get this effectuated, but I do agree with you that it is the

important first step in terms of implementing the Dietary Supplement and Health Education Act. It needs to be done.

Senator DURBIN. What about the other things that Mr. Davis suggested, dosage, limitations of sales to minors, medical supervision——

Dr. CRAWFORD. He is talking about proper dosages, and one of the things we are concerned about with some of these products is since they are natural herbal products, what the potency of them actually is, whether or not they are 25 milligrams per vial or whether they are 65 or whatever. FDA has done some analysis of this in the past, but we are now doing—we have initiated a more comprehensive view of that to see if some of them are super-potent, which would be banned, or if they are sub-potent, which would be fraudulent. So we are going through that now. I assume that is what he means by the establishment of proper dosages.

Under DSHEA, a firm manufacturing a dietary supplement may, without really even notifying the government, change the dosage, so the hold-up in them adopting a dosage that we would recommend should not be complicated. It should be easily done. If he is asking that we think about proper dosages, then that is something we can do, and as a matter of fact, when we proposed the regulation about 5 years ago, we did have, in fact, in that some recommended levels. That regulation was challenged and never did publish. We are still hanging on to part of it and hope to be able to effectuate it.

But there was a lot of commentary about the dosages. We held a public meeting on the subject and we got 14,000 comments and most of them were unfavorable. However, we are committed to ensuring that the proper dosage is on the label and that is one of the reasons we are doing this national analysis that we have undertaken.

Senator DURBIN. I think the question was raised by Dr. Davis of the AMA earlier whether there is a safe dosage. I mean, in over 90 percent of the adverse event reports that we reviewed, people said they took exactly what they were told to take and had a bad reaction to it. I think that was the same question that was raised in Canada, whether there was any way to deal with this in an honest fashion and present this product in a way that wouldn't be harmful.

Dr. CRAWFORD. Yes. I think, certainly with the purified, specific pharmacological product, the ephedrine itself, when used for medical purposes, it is possible to establish the optimal dose, and also the toxic dose has also been established.

With products that may vary in potency like the herbals, it will be more difficult, and I would say—so I don't know the answer to that. I would say this, though, that the worst thing you could say about a compound is that there is no safe level because that basically means it can't be marketed.

As I understand from talking to my Canadian counterparts, they operate under a law that is different from DSHEA, and so essentially they said to the industry that we are not comfortable that you have established that there is a safe dose and, therefore, the product may not be marketed.

Senator DURBIN. Let me see—I am going to draw this to a conclusion. I thank you for your cooperation. Let me make sure I understand as we leave what we have learned from your testimony.

The first is that you have taken some action against a Netherlands manufacturer that is connected with Yellow Jackets and a product called Ecstasy, if I am not mistaken, and some action was taken about their sales in the United States to limit or prohibit sales of their products?

Dr. CRAWFORD. Yes. We have blocked their sales in the United States.

Senator DURBIN. And as far as this particular product, which was the killer for Sean Riggins, you have said that you went—this is Yellow Jackets from——

Dr. CRAWFORD. From NVE.

Senator DURBIN [continuing]. From NVE Pharmaceutical——

Dr. CRAWFORD. Yes.

Senator DURBIN [continuing]. That your agency went to their place of manufacture today in New Jersey, and because of their lack of cooperation you are going to court for authority to get inside to look at their manufacturing practices as well as the information that they have compiled to determine whether action should be taken against them——

Dr. CRAWFORD. Yes.

Senator DURBIN [continuing]. To limit or suspend sales, not only for this product, but also for the product Black Beauty, which they also manufacture——

Dr. CRAWFORD. We will be evaluating Black Beauty, also.

Senator DURBIN. And also, if I am not mistaken, you said that you are near some important threshold when it comes to establishing good manufacturing practices for these DSHEA products, for these nutritional supplements——

Dr. CRAWFORD. Yes, nearer than we have ever been.

Senator DURBIN. Nearer than you have ever been, maybe as many as 4 years away from completion——

Dr. CRAWFORD. That is——

Senator DURBIN. That is the worst case scenario, but——

Dr. CRAWFORD. That is the worst case——

Senator DURBIN [continuing]. This has been one of the worst cases so far, so it could certainly end up that way. And I also understand that in response to letters that I have sent and other activity within your agency, that by the end of November, you will be making your recommendation to Secretary Thompson as to what action should be taken in general in terms of limiting the sale of nutritional supplements containing ephedra, is that correct?

Dr. CRAWFORD. That is correct.

Senator DURBIN. Is there anything that you have left out of here that you want to add into this record so we know what action is being taken by the FDA to protect American consumers?

Dr. CRAWFORD. We are doing this potency study, evaluating what the levels are, and we are particularly concerned about the possibility of super-potency. We are continuing our surveillance of a variety of different firms and products that are in the marketplace, not just ephedra but others that are under DSHEA. So I would say we have stepped up our efforts overall over the last few months

and we will have more announcements to make in that regard. There are some investigations, as you know, including some criminal investigations that I cannot comment on——

Senator DURBIN. And I haven't asked you about them.

Dr. CRAWFORD. Thank you.

Senator DURBIN. I purposely avoided those because I know that that would complicate the situation, which I don't want to do. We thank you for your testimony.

Dr. CRAWFORD. Thank you.

Senator DURBIN. And let me say that your testimony, in addition to that earlier this morning, makes it clear to me that DSHEA is not protecting the American people. We have products that are being sold in this country today that people believe are safe and they are not. We have products that are being sold under false pretenses, that they will achieve some medical result, and they cannot. As a consequence, many people are being deceived in terms of buying these products and some people are dying as a result of these products.

The fact that it takes so long for our Federal Government under this law to even protect the American people, particularly our children, is proof positive this law needs to be changed. I do not favor requiring a prescription for vitamins. That is usually the first line of attack from people in the industry when you suggest changing DSHEA.

But I am in favor of establishing standards, which some have even been acknowledged by the industry, which will provide some standards in terms of manufacture, in terms of the people that are sold these drugs, in terms of the dosage, what is a safe dosage, the representations made as to those dosages, and, going back to Mr. Davis's earlier comments, the need for medical supervision when it comes to some of these nutritional supplements.

All of these things need to be done. All of us have an obligation to do it. Dr. Crawford, you are new to the job. I can't blame you for what came before you and I certainly can't blame you for DSHEA. But those of us in positions of responsibility in Congress have an obligation to the families across this country to do something.

I thank you for your testimony today. I will continue to work with you and Secretary Thompson in the hopes that we can bring some resolution to this as quickly as possible. Thank you very much.

This hearing stands adjourned.

[Whereupon, at 3:16 p.m., the Subcommittee was adjourned.]

APPENDIX

Testimony of Kevin Riggins
October 8, 2002

My name is Kevin Riggins and this is my wife Debbie. The young man in the pictures is our son Sean. On Monday September 2, 2002, Sean complained of an upset stomach, headache and general discomfort. He was to have played in a football game that night, but he sat out due to illness. The following morning my wife took Sean to the doctor's office where Sean was diagnosed with bronchitis. He was given Medication and sent home. That afternoon, Sean began to convulse, and then he stopped breathing. My wife called 911, and proceeded to administer CPR. When the ambulance arrived she called me at work at which time I left and drove 40 miles to the hospital. By the time I arrived my son was gone.

Sean Michael Riggins was born on March 24, 1986 at Minot Air Force Base, North Dakota where I was stationed. From the beginning Sean was an active child, always on the move, never wanting to sit still or take naps. He learned to ice skate at an early age and eventually tried his hand at hockey. Later Sean discovered the martial arts, Tae Kwon Do in particular, where he achieved the rank of Red/Black Belt. Sean has a shelf full of martial arts tournament trophies and was once mentioned in the Tae Kwon Do Times magazine. Later as he got older school sports dominated his time. Wrestling and football were his two greatest passions and he excelled at both sports. In the summer time, his days were usually spent fishing and swimming at the creek, riding his bike and chasing girls. When he got his driver's license he took a part-time job at a restaurant to pay for gas and insurance, and still chased the girls. Sean also liked to go to the YMCA and box, and lift weights. Our son was a very physical person when it came to work and play.

Sean was a very healthy young man as well. There were no heart related problems. Prior to football he had been given a physical and given a clean bill of health. When the coroner told us that Sean had died of a heart attack, it did not seem possible. 16 year old children in good physical health don't just up and die of a heart attack. That was when we found out about ephedrine.

Evidently Sean had been taking a supposed supplement called "Yellow Jackets" to help enhance his performance. He had taken it on Monday for sure, and as we were to find out later, he had taken it more than just the one time. Through our investigation, we have found that Sean's use of ephedrine started during wresting season last year. The Wrestlers would take one or two of these capsules before a meet to" give them an edge." During football it was taken during hell week (double practices) , before games and before big practices when starting positions were being decided. They also started to take these products during sleepovers in order to stay awake. These kids were able to go into a gas station and buy these products right off the shelf. Also about a week after Sean died, the coaches found an empty bottle of Yellow Jackets on the locker room floor. Quite likely someone did not learn a lesson from the death of a teammate. We have

found the use of Ephedrine to be altogether too widespread among the young people today.

Most of the kids today don't realize the danger of these so called supplements. Kids tend to think they are invincible; " that can't happen to me, those things happen to other people." This is the mindset not only of teenagers but of college age students as well. They are taking these products to stay awake for late night partying and cramming for exams. This I found out from one of my supervisors at work. His son told him about ephedrine usage in college. My Son did not take illegal drugs, he did not smoke pot or cigarettes, in fact, when he found out a couple of his friends were doing some of those things he would get after them to quit. These kids have no idea that these products have a very deadly effect.

What I would like to see happen is for these products to be regulated so that a 16--year-old boy or girl cannot go into a gas station or convenient store and purchase them. If these companies have a problem with restricting access to these products so we don't have to bury another child, then they are irresponsible and don't deserve to be in business. We hear an awful lot about homeland security these days, and as a patriot and a veteran, I completely agree with the need to beef it up. But we are charged to protect this nation from all enemies foreign and domestic, and companies that endanger the lives of our young people should be considered enemies and dealt with accordingly. Our kids are our greatest assets and if we have a chance to protect them then I say we do it no matter the cost, because no parent should have to go through this agony, no school children should have to file past their friend lying in a box with hands folded, knowing this is the last image they will have of that person. If I have anything at all to say about it, it won't happen again. Help us make this problem go away, regulate these products so children cannot gain access to them. Thank you.

Testimony of Debbie Riggins
October 8, 2002

Thank you Mr. Chairman for allowing me to testify here today. There are so many still unanswered question for us. It is so hard to come to grips with the death of our son. In what way do these companies differ from drug peddlers? Contract killers? They are making a product; packaging it; wholesaling it; distributing it; having others sell it for them so you don't see their faces; so the common man doesn't know where to go if he has a question or needs help. The only difference that I see is how the law is written or rather no law is in place.

We know that cleaning products are poisonous and can cause physical injury if a child were to get hold of it. It has warning labels. Anyone can buy it. If you give it to a minor who doesn't know any better, chances are good that it will be used in a manner not intended by the manufacturer. Since we know this is a possibility, they've put special caps on them so that the kids can't open them. It's the same with other over the counter medications.

We know that children don't always make the best decisions and so we shield them from some things. We don't allow them to buy cigarettes. We don't allow them to drink alcohol. But this product can be really dangerous.

This product is just one step away from being dispensed from a candy machine next to the Lyons Club Mints. It comes in its snazzy package looking like colorful candy. It isn't expensive, so children can buy it with their pocket-money.

We need to take action to see that children can't access such deadly candy.

Testimony of
Charles Fricke
Logan County Coroner

Before the
U.S. Senate Subcommittee on Oversight of Government Management, Restructuring, and the District of Columbia

Good morning, Mr. Chairman, my name is Chuck Fricke. Thank you for the opportunity to testify before the subcommittee. I am the coroner for Logan County, Illinois and will be testifying regarding the death of Sean Riggins.

It is my determination that the cause of death of Sean Riggins was Acute myocardial infarction. The autopsy revealed a mildly enlarged (410 gram) heart with diffuse softening and mottling of the myocardium. Histologic examination of the heart revealed a dense infiltrate of neutrophils in the myocardium infarction. The coronary arteries arose normally from the aorta, followed a usual course on the surface of the heart, but were of relatively small caliber. No atherosclerosis, thrombus, or other fixed stenosis was in any coronary artery.

Other notable finding at autopsy included an enlarged, congested spleen, fatty change of the liver, small incidental fibrous nodules at the periphery of the lungs, minor abrasions of the right knee and left elbow, and contusions of the left leg.

Toxicology testing revealed lidocaine in the blood, most likely related to cardio-pulmonary resuscitation. No other drugs/ medications were detected in the blood. Toxicology testing of the urine revealed metoclopramide (Reglan), pseudoephedrine and/or ephedrine, and benzyl alcohol. The Reglan detected is consistent with his history of receiving this medication at his doctors office the day he died. The laboratory that performed the testing could not differentiate between pseudoephedrine (a drug found in several over the counter cold and allergy preparations) and ephedrine (a component in several dietary supplements, including "Yellow Jackets"). Benzyl alcohol is a commonly used antibacterial agent in several pharmaceutical preparations. Ephedra alkaloids, including ephedrine, have significant physiologic effects on the cardiovascular system. These effects include elevation of blood pressure and cardiac stimulation. A variety of deaths has been attributed to the effects of ephedrine and includes cases of acute myocardial infarction, likely due to its vasoconstrictive properties.

It is our opinion that the acute myocardial infarct in this individual is consistent with the effects of ephedrine. No other anatomic/structural abnormality of the coronary arteries sufficient to cause myocardial infarction was identified at autopsy. There were no atherosclerotic plagues or acute thrombosis in the coronary arteries. No other drugs, such as cocaine, which may have caused vasospasm of the coronary arteries, were detected in the blood or urine. While we cannot definitively state that ephedrine was detected in the urine (as opposed to pseudoephedrine), this is most likely the case given his history of using "Yellow Jackets" and lack of a reported history the decedent was using preparations containing pseudoephedrine (and lacking ephedrine).

In response to your question asking me of any knowledge of Sean Riggins having a heart condition I found no available information Sean Riggins had prior heart problems. This finding is based on a medical report courtesy of his family physician.

Based on the autopsy there were no other signs as to the cause of death other than ephedrine. This conclusion is related to by the research by city detectives, the school nurse, and Mr. and Mrs. Riggins. This can also be seen from the chemistry results for LD and CK-specific to the heart and liver. CK is the common name for Creaatinine kinase an enzyme release from damaged muscle tissue. A high CK can mean a cardiac event but running a marathon will also increase you CK's. CK is released from damaged cardiac muscle but also from other muscles. A normal level according to the emergency room doctors at Abraham Lincoln Memorial Hospital is anywhere from thirty-eight to one hundred seventy four. Sean Riggins had a CK level of 3500! LD in the liver has a normal range of ninety-one to one hundred and eighty. Sean Riggins had a LD level of 785. His Troponin (enzyme specific to heart muscle) was 100–normal is 1 or 2; heart attack is 4-5. This (Troponin) is a better marker than CK.

The cause of death was consistent with the physiological effects of ephedrine, including its vaso-constrictive properties. The pathologist stated, "We can not definitely state that ephedrine was detected in the urine (as opposed to pseudoephedrine)." Follow up and reports from family, detectives, teammates and the school nurse place *Yellow Jacket's* in Sean's hands. If this is a smoking gun or not, the product was there at sometime.

Yellow Jacket's and ephedra was not something I had seen prior to Sean Riggins' death. My research into *Yellow Jacket's* began when the Lincoln High School nurse, Diane Stephenson made me aware of the students usage. I notified the Lincoln City detectives, John Bunner and Michael Harberts of what I thought to be an illegal drug. Both detectives went to the high school and reuested an interview with the principal, superintendent, and football coach. I drove to the nearest gas station and purchased my own *Yellow Jacket's* and *Stackers*. The label identified it as a diet supplement and High energizer containing twenty-five miligrams ephedra and three hundred miligrams of caffeine. Combien this with drinking *Mountain Dew* or *Code Red* and it would only enhance the caffeine level. Finding out that Sean had not been feeling well and had been vomiting leading to dehydration with little or no food would again enhance the ephedrine as well. The interview with several teammates confirmed that the usage on the team was prevalent and went back to 2001 wrestling team. As the days past after Sean's funeral the students became silent or not wanting to go on record as they feared talking with authorities might lead to blame or arrests. Assurances to the contrary was unsuccessful. I began a dialogue with the parents which they informed me that some of Sean's teammates confided in them when they came to the house. Those stories can best be expressed by them. With the help of the school nurse and a friend of Sean's several students wrote letters confirming their experiences or their parents with Ephedra. Several women at the Lincoln Recreational Center confided they took *Yellow Jacket's* for weight loss and for energy prior to a tread mill exercise. They would also describe the websites and their finding as they searched the Internet.

Since the manufacturers label stated that sales to a minor were prohibited I asked the detectives if they would go to the distributors and request how they enforced sales. They discussed this first with the Logan County States Attorney's office and was informed that the warning was merely the manufacturers and not a state law. He concluded that even a twelve-year-old could purchase them. Most places keep them at the cash register stand and have never requested an age limit. Only in Mt. Pulaski, Illinois, ten miles from Lincoln, Illinois, does the attendant at the local *Market Place* gas station require you to be 18 years of age. When questioned why she does it, her answer was that she had used *Yellow Jacket's* in college prior to going out partying and understood the possible harmful effects ephedra can cause.

W.A.N.D. T.V. in Decatur, Illinois is doing a survey about the public's use of ephedra. They have had numerous calls and will share their results as of Tuesday, October 8, 2002 with me. Decatur, Illinois' Herald and Review's article of October 3, 2002 is asking questions why the NCAA, NFL, Olympic athletes, Canada, and other sports organizations ban Ephedra use and yet a twelve year old in Lincoln, Illinois can purchase it over the counter without being tested in the local schools? As of Tuesday, October 8, 250 calls have been received, with 2 to 1 against ephedra and for legislation.

I have learned much about Ephedra. I've learned like any other lesson in life that if you don't understand it, if the possibilities exist that something may be harmful to you, you shouldn't risk taking it until a more educated and gifted individual in authority test it first. In this case our youth are trusting men and women in the proper authorities that if you have it so readily available over the it must be safe. I have serious questions about this.

This product is easily acquired as twelve year olds can walk into a gas station and purchase it right off the shelf. Mr. Chairman, this concludes my statement, thank you for the opportunity to testify. I would be happy to answer any questions you and the members of the Subcommittee may have.

Written Statement of David W. Brown
President and Chief Executive Officer
Metabolife International, Inc.
Before the Committee on Governmental Affairs
Subcommittee on Oversight of Government Management,
Restructuring, and the District of Columbia
United States Senate
October 8, 2002

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to submit this written statement. I am the President and Chief Executive Officer of Metabolife International, Inc. ("Metabolife"), which markets the nation's leading weight control dietary supplement -- called Metabolife 356®. I would like to take this opportunity to emphasize that my company strongly believes in the science supporting the safety and efficacy of dietary supplements that contain ephedra when used as directed, and also strongly believes that the Food and Drug Administration ("FDA") should issue a science-based regulation (consistent with laws and regulations issued in a number of states) that ensures that ephedra supplements are manufactured and marketed appropriately by all members of the dietary supplement industry.

At the outset, I wish to recognize the Ranking Minority Member of the Subcommittee, Sen. Voinovich, for his role in the Ohio law, which he signed as Governor. Ohio led the nation as its law provided the first comprehensive set of rules for ephedra-based supplements. The Ohio law protects pubic health and preserves the rights of consumers who use these supplements responsibly. Hawaii, Michigan, Nebraska, and Washington have followed Ohio with similar rules (and the Council of State Governments has also issued similar model legislation). As you know, a proposed rule to regulate ephedra-based supplements has been pending at the FDA for the last five years. We believe the American people would be well served if the agency promulgates a rule modeled after the Ohio law.

To date, we are aware of over 30 reports and studies (*See* Attachment A, which contains citations to representative reports and studies) supporting the safety/efficacy of products that contain ephedrine alkaloids - and we believe Metabolife 356® offers consumers a safe, effective way to satisfy their weight-loss objectives.

A recent report (September, 2002) issued by the Federal Trade Commission indicates that the majority of adults in the United States are overweight or obese, and that even the loss of a small amount of weight can prevent and improve many of the medical problems associated with weight gain. The FTC indicated that approximately 61% of U.S. adults are overweight or obese – and that overweight and obesity constitute the second leading cause of preventable death, after smoking, in the United States – resulting in an estimated 300,000 deaths per year.

We at Metabolife are proud that we are helping adult Americans address the important issue of weight loss. Consumers throughout the United States use ephedra dietary supplements as a safe, inexpensive, and effective manner in which to support weight loss, and leading obesity experts have publicly supported the use of these products. In fact, over the last five years, Metabolife has sold over 4.5 billion tablets, or approximately 50 million bottles, of Metabolife 356®.

Although we strongly believe in the safety and efficacy of our products, we are obviously quite sensitive to the concerns that have been expressed regarding the proper marketing and use of dietary supplements containing ephedra. We at Metabolife have been frustrated, however, that the favorable clinical research has been consistently ignored due to the inappropriate legitimacy placed upon anecdotal consumer call records. The General Accounting Office ("GAO") reviewed the "adverse event reports" that the Food and Drug Administration received from consumers, and determined that the reports were unreliable, inconsistent, and could not be used to determine causation. We believe the same logic would apply with regard to Metabolife's anecdotal call records.

The fundamental point is that anecdotal consumer call records cannot and should not substitute for well-controlled scientific studies. In the year 2000, the American Association of Poison Control Centers ("AAPCC") received thousands of reports on health problems associated with aspirin, acetaminophen, and ibuprofen. For example, it is our understanding that in that single year there were over 16,000 reports to the AAPCC involving aspirin, with over 5,000 reports of health problems and over 50 reports of death, over 56,000 reports involving acetaminophen, with over 9,000 reports of health problems and over 90 reports of death, and over 57,000 reports involving ibuprofen, with over 7,000 reports of health problems and over 4 deaths. These data do not suggest any problems with the above products when taken as directed, and do not demonstrate causation. There is no reason to evaluate dietary supplements that contain ephedra any differently.

There should be no doubt that we strongly believe that properly manufactured dietary supplements that contain ephedra are safe when taken as directed on Metabolife's label. To our knowledge, there is not a single well-controlled clinical study that demonstrates that ephedra supplements are unsafe when taken as directed. In addition to the numerous, well-controlled clinical studies that support product safety, many other common-sense facts have been generally ignored in the controversy surrounding ephedra.

First, ephedra contains natural ephedrine alkaloids – and the FDA itself has approved the use of ephedrine in over-the-counter ("OTC") drug products (for asthma) without time limitation at daily dosages 50% higher than that contained in Metabolife 356®. Commonly used OTC drugs contain synthetic ephedrine, and the FDA has indicated that synthetic ephedrine is "generally recognized as safe and effective" at dosages of up to 150 mg/day. Consumers have been safely taking these asthma drug products throughout the past century, and still take these products today. Metabolife 356®, on the other hand, provides a maximum serving limit of 96 mg of ephedrine alkaloids per day.

Second, consumers have been taking drug products that contain synthetic ephedrine alkaloids along with caffeine throughout the past century, and continue to do so today. It has been reported that an average 16 ounce cup of coffee contains 300 mg of caffeine. Consumers with asthma have been safely ingesting coffee, along with ephedrine remedies, for years. Metabolife 356® contains approximately 40 mg of caffeine per tablet, and provides a maximum serving of 320 mg of caffeine per day.

Third, with millions of consumers ingesting any product, it is obvious that some of these consumers will experience health problems that occur widely in the general population. The FDA and HHS – supported by the GAO – have acknowledged that the existence of such anecdotal reports does not demonstrate a cause-and-effect relationship. With regard to ephedra, on June 14, 2002, Secretary

Thompson indicated, in a letter to Public Citizen, that "the FDA has advised me that the types of observed outcomes reported in relationship to the ingestion of ephedrine alkaloids are not uncommon in the general population, and therefore the reports alone do not provide a scientific basis for assessing the safety of ephedrine alkaloids or establish a link between the reported adverse events and the ingestion of ephedrine alkaloids."

Fourth, contrary to what is repeated in news stories around the country, Metabolife has not released 14,700 "adverse event reports" to the FDA. Rather, we released anecdotal consumer call records that do not demonstrate causation, are inconsistent with the favorable background science, and are generally consistent with background levels of health problems in the population. Until the FDA defines the term "adverse event report" for the dietary supplement industry, we believe the term is inappropriate and should not be utilized.

Fifth, ingestion of ephedrine and caffeine for weight-loss purposes is not a new phenomenon. In Denmark, for example, consumers have safely used a weight-loss product (regulated as a drug under the Danish regulatory system) containing synthetic ephedrine and caffeine for the past 12 years.

The above common-sense facts, in conjunction with numerous well-controlled clinical studies, leads us to conclude that Metabolife 356® is safe when taken as directed on the product label. In fact, as part of its ongoing commitment to provide high-quality products to consumers, Metabolife has been: (1) actively monitoring the science surrounding ephedra and caffeine combinations, (2) committing to support the Department of Health and Human Services ("HHS") and the National Institutes of Health ("NIH") in their efforts to further research ephedra, (3) implementing quality assurance procedures (such as voluntary batch testing of each lot of product produced to ensure consistency with label claims) that far exceed those required by the FDA for dietary supplements, (4) taking affirmative steps to communicate that ephedra products are not for everyone and by informing consumers regarding proper use and stating that individuals with certain pre-existing conditions should consult a health practitioner prior to product use, and (5) actively pursuing stringent, science-based ephedra legislation, or regulation, to require all ephedra products to be marketed and manufactured responsibly and taken as directed.

Metabolife is aware of over 30 reports and studies supporting the safety/efficacy of products that contain ephedrine alkaloids (*See* Attachment A). Those studies include the recent Harvard/Columbia trial, a well-controlled, six-month study of 167 mildly to severely overweight adults. That trial found that the herbal combination produced only mild side effects, when compared to placebo, and that the data was consistent with the known mechanisms of action of ephedrine and caffeine and the large number of studies conducted on synthetic ephedrine and caffeine. The study also demonstrated that the ephedra/caffeine combination was more effective than placebo in reducing body weight, body fat, and waist and hip circumference -- subjects in the ephedra/caffeine group lost an average of 11.7 pounds (5.3 kg) during the study, compared to an average of 5.7 pounds (2.6 kg) in the placebo group. (*See* Attachment B).

The scientific evidence, including the clinical trials and a comprehensive safety review conducted by Cantox Health Sciences International, supports the conclusion that properly manufactured ephedra dietary supplements are safe when taken as directed on Metabolife's label. Indeed, ephedra has been consumed safely worldwide for over 5,000 years. Moreover, as noted, FDA has previously found that synthetic ephedrine is "generally recognized as safe and effective" at dosages of 150 mg/day in over-the-counter ("OTC") drugs, such as asthma remedies, without time limitation.

Metabolife believes in ephedra's existing safety record. Moreover, Metabolife supports HHS's funding of the RAND Corporation to conduct a comprehensive review of the existing science on ephedra, and NIH for its intent to use the RAND study as a guide to expand research efforts on ephedra. To assist the government in these efforts, Metabolife has publicly committed to supporting, financially and otherwise, and urging others in the industry to support, a blue ribbon commission established by HHS or NIH to supervise one or more further long-term clinical studies of the safety and efficacy of ephedra/caffeine combinations for weight control.

In addition, Metabolife has taken proactive steps to ensure that Metabolife 356® actually contains what the label claims it contains. Despite the fact that Good Manufacturing Practices ("GMPs") for dietary supplements have yet to be issued, Metabolife has implemented quality control procedures, such as batch-testing, that exceed the GMPs for food. Metabolife's labeling also clearly states that the product should not be sold to minors; it recommends serving limits consistent with the levels that scientific studies have shown to be safe; and it has a stringent warning statement to advise people with certain pre-existing medical conditions against taking the product without consulting a health care professional. Moreover, Metabolife has committed, in its August 15, 2002, letter to Secretary Thompson, to prepare to lead an industry-wide consumer information campaign to warn against abuses of ephedra products, especially by young athletes and minors, and to urge all consumers to read the label carefully.

Unfortunately, although it is our understanding that many companies market products responsibly, ephedra supplements have been promoted to individuals, including minors, as street drug alternatives under such brand names as *Herbal Ecstacy, Black Beauties, Yellow Jackets, Herbal Coke, Magic Mushrooms*, and *Cloud 9*. We believe marketing dietary supplements as alternatives to "street drugs," or in ways that encourage abuse, is unacceptable. We call on the regulatory authorities to stop this outrageous conduct, and bring enforcement actions against such companies immediately. We also support the FDA for its recent actions against companies that sell dietary supplements that contain synthetic ephedrine alkaloids.

Because ephedra supplements are not for everyone, we strongly support a science-based, FDA regulation that would place limits on promotional claims, mandate serving limits, and generally require companies to act responsibly when manufacturing and selling their products. Accordingly, Metabolife has been advocating stringent, science-based ephedra legislation, or regulation, to require all ephedra products to be marketed and manufactured responsibly and taken as directed. Metabolife's proposal includes the following provisions:

- **Ban on Illicit Drug Claims –** Metabolife's proposal includes a prohibition on the promotion of ephedra products as alternatives to illicit drugs.

- **Ban on Sale to Minors** – Metabolife's proposal prohibits the sale of food and dietary supplements containing ephedra to individuals under the age of 18.

- **Ban on Synthetic Ephedrine Alkaloids –** Metabolife's proposal prohibits the sale of food and dietary supplements containing synthetic ephedrine alkaloids.

- **Mandatory GMPs** – Metabolife's proposal requires FDA to expedite GMPs for dietary supplements, and it requires manufacturers of ephedra dietary supplements to implement quality assurance programs, such as the batch-testing program already used by Metabolife, to ensure that ephedra products contain what they claim to contain.

- **Strict Labeling Statements** –Metabolife's proposal includes a strict warning statement providing that individuals with pre-existing medical conditions, such as heart or thyroid disease, should consult a physician or licensed qualified health care practitioner prior to product use.

- **Strict Science-Based Serving Limits** – Metabolife's proposal requires serving limits (up to 25 mg/serving and up to 100 mg/day) that are consistent with the results of a number of studies, including the Harvard/Columbia trial. There is an emerging science-based consensus that these limits are safe among an increasing number of states (including Hawaii, Michigan, Nebraska, Ohio, and Washington). These states have already adopted ephedra legislation or regulations that incorporate these limits.

- **Mandatory Manufacturer Reporting to the FDA** – Metabolife supports mandatory industry-wide reporting to the FDA. In fact, to our knowledge Metabolife is the first and only dietary supplement company to voluntarily provide its consumer call records to the FDA.

- **Full Disclosure on Product Label** -- Metabolife's proposal requires the labels on food and dietary supplements containing ephedra to disclose: (1) the amount of ephedra in each serving (and the amount of product that constitutes a serving), (2) that taking more of the product than recommended (or taking it at greater frequencies) may increase the risk of negative health experiences, and (3) that the maximum recommended daily dose of ephedra is 100 mg.

- **Consumer-Friendly Reporting** – Metabolife's proposal would require labels on food and dietary supplements containing ephedra to list a toll free number for consumer inquiries that is maintained by the manufacturer, distributor, retailer, or third-party. Alternatively, we support listing the FDA MedWatch number on product labels.

Finally, we at Metabolife would like to question whether it is good policy for the government to criticize a company for: (1) providing consumers with access to a voluntary help-line; and (2) voluntarily maintaining consumer call records. In establishing a voluntary help-line and maintaining these records, we engaged in unprecedented supportive actions for a dietary supplement company. We question whether any FDA-regulated company will ever again voluntarily maintain a help-line and maintain consumer records based upon the reaction we have received.

We thank you again for the opportunity to provide this information. Metabolife will continue to provide you and others with information like this that is based upon the best information available to us.

ATTACHMENT A

A. Reports

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Attachment B

International Journal of Obesity (2002) 26, 593–604

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PAPER

Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial

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OBJECTIVE: To examine long-term safety and efficacy for weight loss of an herbal Ma Huang and Kola nut supplement (90/192 mg/day ephedrine alkaloids/caffeine).
DESIGN: Six-month randomized, double-blind placebo controlled trial.
SUBJECTS: A total of 167 subjects (body mass index (BMI) 31.8 ± 4.1 kg/m^2) randomized to placebo (n = 84) or herbal treatment (n = 83) at two outpatient weight control research units.
MEASUREMENTS: Primary outcome measurements were changes in blood pressure, heart function and body weight. Secondary variables included body composition and metabolic changes.
RESULTS: By last observation carried forward analysis, herbal *vs* placebo treatment decreased body weight (− 5.3 ± 5.0 *vs* − 2.6 ± 3.2 kg, $P < 0.001$), body fat (− 4.3 ± 3.3 *vs* − 2.7 ± 2.8 kg, $P = 0.020$) and LDL-cholesterol (− 8 ± 20 *vs* 0 ± 17 mg/dl, $P = 0.013$), and increased HDL-cholesterol (+2.7 ± 5.7 *vs* − 0.3 ± 6.7 mg/dl, $P = 0.004$). Herbal treatment produced small changes in blood pressure variables (+3 to − 5 mmHg, $P \leq 0.05$), and increased heart rate (4 ± 9 *vs* − 3 ± 9 bpm, $P < 0.001$), but cardiac arrhythmias were not increased ($P > 0.05$). By self-report, dry mouth ($P < 0.01$), heartburn ($P < 0.05$), and insomnia ($P < 0.01$) were increased and diarrhea decreased ($P < 0.05$). Irritability, nausea, chest pain and palpitations did not differ, nor did numbers of subjects who withdrew.
CONCLUSION: In this 6-month placebo-controlled trial, herbal ephedra/caffeine (90/192 mg/day) promoted body weight and body fat reduction and improved blood lipids without significant adverse events.
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Keywords: Ma Huang; Kola nut; ephedrine; ephedra alkaloids; obesity; weight loss; clinical trial; herbal medicine; alternative medicine

Introduction

Since passage of the Dietary Supplement Health and Education Act (DSHEA) by Congress in 1994, classifying herbal compounds as 'dietary supplements', marketing of such products in the USA has escalated. Sales are estimated to have risen from $9.8 billion in 1995 to $14.7 billion in 1999.[1] A large portion of that market is devoted to herbal dietary supplements containing ephedra, with three billion servings reportedly sold[2] and approximately 12 million individuals estimated to be using such products in 1999.[2] While the consequence of DSHEA is that the Food and Drug Administration (FDA) does not regulate the sales of these products, the FDA does collect anecdotal reports of adverse events and these reports have raised concerns about the safety of ephedra products by the FDA[3] and the media.[1,4,5]

A major reason for use of ephedra-containing herbal products is body weight reduction. Questions of safety and efficacy are central issues for any agent used for human weight control. Ephedrine, the primary active ingredient of herbal ephedra, has been well studied both alone, and in combination with caffeine. Placebo-controlled studies have demonstrated that ephedrine, particularly in combination

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with caffeine, is effective in promoting weight loss without increasing serious adverse events[6–9] and the combination is used for that purpose in Europe.[10] Despite this literature for synthetic ephedrine, the lack of data demonstrating similar effects for herbal ephedra has contributed to questions of both its safety and efficacy.[2]

Two clinical trials demonstrating efficacy of herbal ephedra combinations for reduction of body weight and fat have been completed.[11,12] Both studies, however, were only 8 weeks in duration, thus limiting conclusions about longer-term safety. The purpose of the present 6 month study was to provide objective assessment of safety and efficacy for weight-loss of a herbal dietary supplement containing Ma Huang herbal ephedra and Kola nut (as sources of ephedrine alkaloids and caffeine). While the emphasis of the present investigation was on the detailed monitoring of blood pressure, heart rate and disrhythmias during the acute phase of treatment, this study is also the first reported long-term, clinical trial of a herbal preparation containing ephedrine alkaloids and caffeine in combination.

Methods

Study design

The study was a prospective, two-arm, 6-month, randomized, double-blind, placebo-controlled, clinical safety and efficacy trial conducted at two sites (New York and Boston). Efficacy was assessed by measuring changes in body weight, body fat and waist and hip circumferences. Safety was assessed by determining changes in cardiovascular parameters, blood chemistries, liver enzymes, self-reported symptoms and reasons for withdrawal from the study.

Randomization of equal numbers of subjects to placebo or herbal groups was achieved using a random number table, with block sizes varying between two and eight. A statistician not involved in the study produced separate randomization codes for the two sites. Sealed copies of these codes were provided to the investigators for emergency identification. Otherwise, codes remained sealed until completion of the study, when another statistician, who was not involved in carrying out the study, was provided with the code and the data for analysis.

Statistical analyses were designed on an 'intention-to-treat' basis to achieve a statistical power of 0.90 and a 0.05 type I error for a two-sided test. Power calculations were primarily concerned with the possibility of adverse effects during the acute phase of the study (weeks 1–4). Using a two-sample *t*-test, a minimum of 66 subjects in each group would have been sufficient to detect a difference of 4.1 mmHg systolic blood pressure (s.d. = 7.23), a difference of 4.6 mmHg diastolic blood pressure (s.d. = 6.0), and also a difference in heart rate of 6 bpm (s.d. = 10.36). The study was approved by the Institutional Review Boards of St Luke's-Roosevelt Hospital Center in New York and Beth Israel Deaconess Medical Center in Boston and all subjects gave written consent prior to participation.

Subjects

Subjects, recruited by advertisements in local newspapers and flyers, were interviewed by telephone. Eligibility requirements included age between 18 and 80 y and body mass index (BMI) ≥ 25 and $\leq 40\,kg/m^2$. Subjects were recruited without regard to racial or ethnic background. Smokers were not excluded, nor were diabetics with reasonable control (hemoglobin A1C $\leq 7.8\%$) who did not take insulin or oral diabetic medication. Subjects were excluded if they were not otherwise healthy, were pregnant or nursing, had recently lost weight or participated in other diet or drug studies, or if they reported consumption of $> 500\,mg$/day caffeine (see Appendix I for complete list of exclusions).

For inclusion in the study, subjects were required to successfully pass a medical screening by a study physician. This included medical history and symptom evaluations, a physical examination that included measurement of height and weight, sitting blood pressure and pulse rate, an EKG and a laboratory evaluation including blood test and urine toxicology screen. Subjects were not included if blood pressure was $\geq 140/90$ or if values from laboratory tests were outside normal ranges. Screening also included 24 h measurement of blood pressure by ambulatory blood pressure monitor (ABPM) and heart rhythm by Holter monitor. Subjects were excluded if monitoring detected hypertension (defined as mean 24 h systolic BP $\geq 139\,mmHg$ or mean 24 h diastolic BP $\geq 87\,mmHg$) or significant ventricular ectopy (including > 1000 premature beats/24 h, 'R on T' phenomenon, torsades de pointes, or QT interval prolongation; runs of supraventricular tachycardia > 1 min, or new onset atrial fibrillation; or presence of any other clinically significant rhythm disturbance). Holter data and EKGs of subjects with multiform or multifocal ventricular events (MFVE) were reviewed by the study cardiologist prior to admission. Those without evidence of other significant cardiac disease were allowed to enroll in the study.

Following successful medical screening, subjects returned within 1–4 weeks for a baseline evaluation that included repeat measurements of height, weight, sitting blood pressure and heart rate as well as measurement of waist and hip circumferences and body fat. The symptom questionnaire was again completed and ABPM and Holter monitors worn for a second 24 h period. Subjects who did not fall into any of the exclusion categories after these baseline measures were randomized to either placebo or the herbal preparation (Ma Huang/Kola nut).

Treatment

At randomization, subjects were counseled to eat normally, but limit intake of dietary fat to 30% of calories and to exercise moderately (eg walking 30 min/day, three times a week). Handouts on good eating habits and a progressive walking/exercise program were provided. Active and placebo tablets were supplied in opaque white plastic bottles containing a known number of tablets. Subjects were directed to take

two tablets, 30 min before each meal, three times a day (six tablets per day, the maximum amount recommended on most ephedra-containing commercial products) and to return unused pills, which were counted to determine adherence.

The active preparation was a herbal mixture (provided by Science, Toxicology and Technology, San Francisco, CA, USA) containing Ma Huang (NutraTech Inc, Gardena, CA, USA) and Kola nut (Ashland Distribution Corp, Santa Anna, CA, USA) as the only active ingredients. Each tablet was specified to contain 15 mg of total ephedrine alkaloids and 32 mg of caffeine per tablet, for a total daily amount of ephedrine alkaloids and caffeine of 90 and 192 mg, respectively. The placebo was an identical appearing tablet containing inert ingredients. Certificates of analyses for ephedrine alkaloid and caffeine content provided to the supplier were validated by the investigators.

During the initial month of treatment, subjects returned weekly to pick up pills, review dietary and exercise advice, complete the symptom questionnaires and have weight, sitting blood pressure and pulse rate measured. At weeks 1, 2 and 4, ABPM and Holter monitors were worn for additional 24 h periods. At the end of the first month, another blood sample was taken for assessment of ALT, creatinine and HCG (in women of child-bearing age).

During the subsequent 20 weeks, subjects returned every 4 weeks for a 30 min visit. The symptom questionnaire was completed, and a brief dietary and symptom review and physical evaluation by the study coordinator including weight, sitting blood pressure and heart rate was taken. Blood was taken for ALT, creatinine and HCG (in women of child-bearing age) at each of these visits.

At week 12 and 24 (final) visits, additional fasting blood samples were taken, EKGs recorded, and measurements of waist and hip circumferences and body fat content repeated.

Measurements

Medical and nutrition history and self-reported symptoms were evaluated by questionnaires designed by the investigators (PAD & TM) for this study. Height was measured to the nearest 0.5 cm by stadiometer (Holtain, Crosswell, Wales, UK). Body weight was measured to the nearest 0.1 kg using a digital scale (NY site: Weight Tronix, New York, USA; Boston site: Detecto-Medic, Detecto Scales Inc, Brooklyn, NY, USA). Trained personnel measured waist and hip circumferences at standard anatomical locations.[13] Total body fat was assessed by bioimpedance (Tanita Inc: TBF 310, Arlington Heights, IL, USA). Siri's two-compartment model was used to convert measured body density to fat.[14]

Blood studies included serum glucose and lipids (cholesterol and triglycerides), liver and renal function tests (creatinine, ALT and AST), TSH, standard electrolytes, a complete blood count (NY site: Quest Diagnostic Laboratory, Teterboro, NJ, USA; Boston site: Veterans Admistration North Texas Health Care System, Dallas, TX, USA). Toxicologic urine screens (see Appendix II for list of tests) were performed by Diagnostic Laboratories, Vanderbilt University Medical Center, Nashville, TN, USA.

Data from Holter and ABPM monitors were analyzed by Space Laboratories (Seattle, OR, USA), with follow-up evaluations as required by the study cardiologist. EKGs of the NY subjects were evaluated for four intervals (RBR, P-R, QT_c QRS), QRS amplitude and cardiac rhythm.

Three independent laboratories (Alpha Chemical and Biomedical Laboratories, Petaluma, CA, USA; Industrial Laboratories Company Inc, Denver, CO, USA; and San Rafael Chemical Services, Salt Lake City, UT, USA) analyzed samples of active and placebo tablets by high pressure liquid chromatography (HPLC) for ephedrine, total ephedrine alkaloids and caffeine.

Statistical methods

Values are presented in the text and tables as mean ± standard deviation (s.d.) and in the figures as means ± standard errors (s.e.). The tables show statistical comparisons between the groups by the 'last observation carried forward' (LOCF) method for dealing with missing data. Values for subjects who dropped out after the acute phase (week 4) were carried forward to each subsequent time point in the trial. Figures present analyses of only data that was actually available for subjects at each time point, with no values carried forward for subjects who dropped out.

Effect of treatment on weight, body fat, waist and hip circumferences, sitting blood pressure, heart rate and blood chemistries were assessed by using a repeated measures ANOVA test for group by time interaction, followed by pair-wise *t*-tests. Repeated categorical data (eg cardiac arrhythmias) were analyzed using a weighted least squares model (WLS)[15] followed by pair-wise chi-square tests, where possible. Reasons for withdrawal in each group were compared using chi-square tests. All analyses were conducted using a two-tailed 0.05 alpha level.

Results

Subject disposition

Of 284 subjects who appeared eligible by telephone screen, 167 were randomized (83 to ephedra/caffeine and 84 to placebo; Figure 1). Of those not randomized, most either chose not to participate (45) or were ineligible due to violations of protocol inclusion requirements (15) or non-compliance with protocol requirements (8). Thirty-one were ineligible for medical reasons that were exclusionary for the protocol.

During the first 4 weeks of the study, the acute phase, 17 (20%) randomized subjects withdrew from each group, with 66 remaining in the herbal group and 67 remaining in the placebo group. During the remaining 5 months of the study, there were 20 (24%) withdrawals from the herbal group and 26 (31%) from the placebo group.

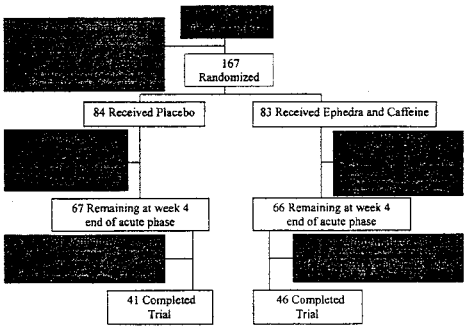

Figure 1 Disposition of all subjects recruited for the study.

Baseline physical characteristics of subjects

Subjects in the two treatment groups (P, placebo: H, herbal) did not differ ($P > 0.05$) initially in age (46.0 ± 12.2 (mean ± s.d.); 44.5 ± 12.4 y), body weight (88.1 ± 14.8; 87.9 ± 13.9 kg), or BMI (31.7 ± 4.0; 31.8 ± 4.4 kg/m^2; Table 1). Distributions of gender and self-identified race were also not significantly different between groups (P, 86% female; H, 78% female; (P, 70% Caucasian, 15% African-American and 7% Hispanic; H, 69% Caucasian, 11% African-American and 12% Hispanic).

Herbal analysis

Independent laboratory HPLC analysis detected, per placebo tablet, less than 0.3 mg (range, non-detectable to < 0.3 mg) each of caffeine and total ephedrine alkaloids and, per herbal tablet, 32.7 ± 1.5 mg caffeine and 14.4 ± 1.6 mg total ephedrine alkaloids.

Table 1 Baseline characteristics of all randomized subjects

Characteristic	*Placebo (n = 84)*	*Herbal (n = 83)*
Gender		
Men (*n* (%))	12 (14%)	18 (22%)
Women (*n* (%))	72 (86%)	65 (78%)
Race (*n* (%))		
Caucasian	59 (70%)	57 (69%)
African-American	13 (15%)	9 (11%)
Hispanic	6 (7%)	10 (12%)
Indian, Asian, Other	5 (6%)	6 (7%)
	X ± s.d.	X ± s.d.
Age (y)	46.0 ± 12.2	44.5 ± 12.4
Weight (kg)	88.1 ± 14.8	87.9 ± 13.8
Body mass index (kg/m^2)	31.7 ± 4.0	31.8 ± 4.4

Race was by self-identification. One subject in each group did not identify race.

Adherence

Adherence, calculated as the percentage of pills not returned by the subject relative to the number of pills supplied, did not differ between groups (P, 90 ± 11%; H, 89 ± 10%).

Treatment effects

Body weight and body composition. Results of LOCF analyses of physical values are shown in Table 2. Both treatment groups lost significant ($P < 0.001$) amounts of body weight and body fat over the 6 months of the study. Losses in the herbal group, however, were greater than in the placebo for both body weight (H, − 5.3 ± 5.0; P, − 2.6 ± 3.2 kg; $P < 0.001$) and body fat (H, − 4.3 ± 3.3 kg, P, − 2.7 ± 2.8 kg, $P = 0.020$).

Both groups also had significant decreases in waist (P, − 2 ± 6 cm, $P = 0.004$ and H, − 6 ± 5 cm, $P < 0.001$) and hip circumferences (P, − 4 ± 4 cm, $P < 0.001$ and H, − 6 ± 5, $P < 0.001$), but again these changes were significantly greater in the herbal *vs* the placebo group for both waist ($P = 0.005$) and hip circumferences ($P = 0.018$). There were no significant interactions or differences between the treatment groups in waist-hip ratio (not shown).

Mean values for all subjects for whom data were collected at each time point are shown for body weight in Figure 2 and for body fat in Figure 3. Of subjects who completed the 6-month study, those in the herbal group lost significantly more body weight than those in the placebo group (P, − 3.1 ± 4.0; H, − 7.0 ± 4.3 kg; $P < 0.001$). Body fat was also significantly decreased by herbal treatment for subjects with

Table 2 LOCF analysis of physical values[a]

Measure	Study period	Group: Placebo X ± s.d. (P-value)[b]	Group: Herbal X ± s.d. (P-value)[b]	P[c]
Body weight (kg)	Baseline	87.9±13.9	88.1±14.8	0.955
	6 month	85.3±14.7	82.8±15.4	0.319
	Change	−2.6±3.2 (<0.001)	−5.3±5.0 (<0.001)	<0.001
	ANOVA	Time×group interaction: $P<0.001$		
Body fat mass (kg)	Baseline	34.2±9.9	32.6±9.1	0.451
	6 month	31.5±10.6	28.2±9.2	0.150
	Change	−2.7±2.8 (<0.001)	−4.3±3.3 (<0.001)	0.020
	ANOVA	Time×group interaction: $P<0.020$		
Waist circumference (cm)	Baseline	98±12	97±13	0.699
	6 month	96±13	92±13	0.135
	Change	−2±6 (0.004)	−6±5 (<0.001)	0.005
	ANOVA	Time×group effect: $P=0.004$		
Hip circumference (cm)	Baseline	117±10	115±9	0.270
	6 month	113±10	109±10	0.033
	Change	−4±4 (<0.001)	−6±5 (<0.001)	0.018
	ANOVA	Time×group effect: $P=0.044$		
Systolic blood pressure (mmHg)	Baseline	120±11	119±11	0.877
	6 month	120±12	118±12	0.405
	Change	0±11 (0.659)	−1±9 (0.289)	0.313
	ANOVA	Time×group interaction: $P=0.177$		
Diastolic blood pressure (mmHg)	Baseline	79±8	77±6	0.365
	6 month	79±9	78±9	0.397
	Change	0±8 (0.729)	<1±8 (0.836)	0.928
	ANOVA	Time×group interaction: $P=0.128$		
Heart rate (bpm)	Baseline	74±7	69±8	0.001
	6 month	71±9	73±10	0.130
	Change	−3±9 (0.008)	4±9 (0.001)	<0.001
	ANOVA	Time×group interaction: $P<0.001$		

[a]Treatment was a herbal supplement containing 90 mg ephedra and 192 mg caffeine/day ($n=69$/group for weight, SBP, DBP, heart rate; $n=38$ for placebo and 39 for herbal for body fat; $n=48$ for placebo and 47 for herbal for waist and hip).
[b]P-value for within-group change from baseline compared by paired samples t-test.
[c]Treatment vs placebo groups were compared by ANOVA test for group×time interaction followed by pair-wise t-tests of baseline and 6 month values and change from baseline at 6 months, with alpha set at 0.05.

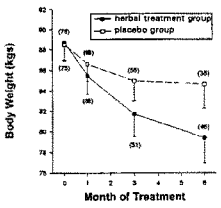

Figure 2 Effect of herbal and placebo treatment on change in body weight. Values shown include all subjects in herbal and placebo treatment groups for whom there was data at each time point (n).

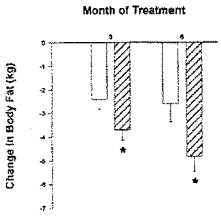

Figure 3 Change in body fat from baseline after 3 months and 6 months of herbal or placebo treatment. Open bars represent placebo ($n=38$ at 3 months, $n=25$ at 6 months). Hatched bars represent herbal treatment ($n=39$ at 3 months, $n=26$ at 6 months). *$P \leq 0.05$.

complete body composition data at 3 months (P, −2.4±2.6 kg; H, −3.7±2.6 kg, $P=0.031$) and 6 months (P, −2.6±3.9 kg; H, −4.8±3.2 kg, $P=0.032$).

Blood pressure and heart rate at office visits. Mean systolic and diastolic blood pressure measurements did not differ between treatment groups at any time point, nor was there a significant group-by-time interaction for either variable, whether analyzed by LOCF (Table 2) or using all available data (not shown). Change in heart rate was significantly different ($P<0.001$) between groups (P, −3±9, $P=0.008$; H, 4±9, $P<0.001$). Time-by-group interaction was also significant ($P<0.001$), with values in the herbal group compared with placebo that were lower at baseline (by 4±3.9 bpm, $P=0.001$), but not significantly different (4 bpm±3.9, $P=0.130$) at 6 months (Table 2, LOCF). Analysis of all available data for heart rate showed similar results to LOCF analysis, with a significant time-by-group interaction ($P<0.001$), and differences between groups that were significant only at baseline (when H was lower than P, $P<0.01$) and at 3 months (when H was higher than P, $P<0.05$; not shown).

Treatment groups did not differ in EKG data, analyzed at the NY site, for any of the four intervals evaluated (RR, P-R, QTc, QRS) or for QRS amplitude and heart rhythm (not shown).

Blood pressure by 24 h monitor. Data from 24 h monitors at baseline, and weeks 1, 2 and 4 were compared for 24 h mean, daytime mean (6:00 am to midnight) and night-time mean (midnight to 6:00 am), for SBP, DBP, minimum SBP and DBP, maximum SBP and DBP and mean arterial pressure (Table 3).

Effects of herbal treatment on blood pressure were small, but time-by-group interactions were statistically significant ($P\leq0.05$) for: 24 h averages of SBP, DBP and minimum SBP; and for daytime averages of SBP and minimum SBP. Maximum increases over baseline at 4 weeks in the herbal group

Table 3 Twenty-four-hour ambulatory blood pressure monitor data

		24 h average			*Day (6:00 am – midnight)*			*Night (midnight – 6:00 am)*		
		Placebo	*Herbal*	*P*	*Placebo*	*Herbal*	*P*	*Placebo*	*Herbal*	*P*
SBP (mmHg)	B	118±8	120±8	0.403	120±8	121±8	0.602	108±8	110±9	0.179
	W1	118±8	118±8	0.754	120±9	119±10	0.462	108±10	110±11	0.230
	W2	116±8	118±8	0.133	118±8	120±8	0.251	106±9	111±10	0.005
	W4	116±11	120±9	0.020	118±11	121±8	0.060	107±10	111±10	0.014
	ANOVA	Time×group interaction: $P=0.016$			Time×group interaction: $P=0.021$			Time×group interaction: $P=0.152$		
DBP (mmHg)	B	72±7	72±6	0.887	74±7	73±6	0.252	63±6	63±7	0.991
	W1	72±10	72±7	0.637	74±7	73±6	0.340	64±8	65±8	0.646
	W2	71±10	73±7	0.200	74±7	74±6	0.895	63±7	64±9	0.193
	W4	71±11	75±8	0.056	74±8	76±11	0.251	61±10	65±10	0.015
	ANOVA	Time×group interaction: $P=0.020$			Time×group interaction: $P=0.053$			Time×group interaction: $P=0.066$		
MINSBP (mmHg)	B	95±7	95±8	0.766	98±8	98±8	0.454	98±8	99±10	0.277
	W1	94±9	95±10	0.729	98±11	98±11	0.991	97±10	100±11	0.160
	W2	91±9	95±9	0.030	95±11	99±10	0.035	94±10	99±10	0.004
	W4	93±10	97±10	0.012	96±12	101±10	0.021	96±10	100±11	0.043
	ANOVA	Time×group interaction: $P=0.008$			Time×group interaction: $P=0.017$			Time×group interaction: $P=0.257$		
MINDBP (mmHg)	B	50±6	49±8	0.400	53±7	53±8	0.798	52±7	54±8	0.263
	W1	52±7	49±9	0.116	54±7	54±10	0.819	54±8	55±8	0.695
	W2	51±6	50±10	0.606	54±7	54±8	0.917	52±7	52±9	0.884
	W4	50±7	51±9	0.576	54±8	55±8	0.552	52±7	54±9	0.323
	ANOVA	Time×group interaction: $P=0.089$			Time×group interaction: $P=0.868$			Time×group interaction: $P=0.652$		
MAXSBP (mmHg)	B	143±12	143±11	0.741	142±12	143±11	0.922	119±9	122±11	0.077
	W1	142±13	141±12	0.917	141±13	141±12	0.713	119±12	121±13	0.370
	W2	140±12	141±10	0.591	140±12	141±10	0.835	117±12	121±13	0.046
	W4	140±14	140±13	0.716	140±14	138±21	0.559	118±12	122±12	0.078
	ANOVA	Time×group interaction: $P=0.941$			Time×group interaction: $P=0.803$			Time×group interaction: $P=0.683$		
MAXDBP (mmHg)	B	93±8	93±10	0.969	93±9	93±9	0.991	72±8	73±10	0.859
	W1	94±11	92±8	0.104	94±12	92±7	0.156	75±10	74±7	0.339
	W2	92±8	92±10	0.885	92±8	91±8	0.388	73±9	73±8	0.991
	W4	94±12	93±8	0.576	94±12	92±8	0.295	73±10	76±10	0.044
	ANOVA	Time×group interaction: $P=0.433$			Time×group interaction: $P=0.605$			Time×group interaction: $P=0.059$		
MAP (mmHg)	B	87±6	87±6	0.877	90±6	90±6	0.537	79±6	79±7	0.649
	W1	86±7	86±6	0.452	90±8	89±8	0.697	80±8	80±7	0.987
	W2	85±7	85±6	0.920	89±7	89±5	0.981	78±8	80±7	0.134
	W4	85±8	86±7	0.473	89±9	90±6	0.494	78±8	80±8	0.076
	ANOVA	Time×group interaction: $P=0.271$			Time×group interaction: $P=0.452$			Time×group interaction: $P=0.175$		

SBP, systolic blood pressure; DBP, diastolic blood pressure; MINSBP, minimum systolic blood pressure; MINDBP, minimum diastolic blood pressure. MAXSBP, maximum systolic blood pressure; MAXDBP, maximum diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate. S, Screen (prior to treatment); B, baseline (prior to treatment); W1, W1, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n=67$) or placebo (P, $n=66$).

were 3 mmHg (day DBP, day min SBP, both $P=0.02$) and significant ($P \leq 0.05$) decreases occurred in max SBP for both 24 h and day averages (-3 and -5 mmHg). Most of the differences in change over time were due to decreases in the placebo group, with small or no change in the herbal group. There were no statistically significant time-by-group interactions for minimum DBP, for maximum SBP or DBP or for mean arterial pressure.

Holter monitor data. As shown by office visit measurements, there was a significant time-by-group interaction ($P=0.020$) for heart rate assessed by Holter monitor. Between-group differences were significant ($P<0.05$) only at baseline, when the heart rate of the herbal group was lower by 3 bpm (Table 4). Heart rate over the 4 weeks of Holter measurement increased by 1 ± 14 bpm in the herbal group *vs* a decrease of 5 ± 13 bpm in the placebo group ($P=0.026$).

None of the cardiac arrhythmias assessed were increased by herbal treatment. The only significant time-by-group interaction ($P<0.024$), for percentage of subjects displaying incidents of bradycardia (≤ 60 bpm) was due to a decrease in the herbal group (-12%, *vs* no change in the placebo group). Ventricular events/h did not differ between groups at any time point, nor did the percentage of subjects with tachycardia (≥ 100 bpm), MFVEs or runs of ventricular events.

Blood chemistries. By LOCF analysis, there were statistically significant 6-month improvements with herbal treatment in serum levels of total cholesterol (-6 ± 23 mg/dl, $P=0.03$), LDL-cholesterol (-8 ± 20 mg/dl), HDL-cholesterol ($+3 \pm 6$, $P=0.0001$), and triglycerides (-12 ± 41 mg/dl, $P=0.01$), with no change in blood glucose (0 ± 10 mg/dl, $P=0.68$; Table 5). These changes were significantly different from placebo, however, only for LDL-cholesterol, HDL-cholesterol and glucose. The difference in change in serum levels

Table 4 LOCF analysis of Holter monitor data

		Group		
Measure	*Study period*	*Placebo*	*Herbal*	P
Pulse, average bpm/24 h ± s.d.	Baseline	78 ± 8	75 ± 11	0.050
	Week 1	74 ± 10	77 ± 12	0.169
	Week 2	74 ± 10	77 ± 12	0.211
	Week 4	73 ± 12	76 ± 14	0.370
	ANOVA	Time×group interaction: $P=0.020$		
Ventricular events/h, median (inter-quartile range)	Baseline	0.08 (0.57)	0.06 (0.14)	0.188
	Week 1	0.04 (0.29)	0.00 (0.13)	0.129
	Week 2	0.06 (0.44)	0.04 (0.29)	0.400
	Week 4	0.04 (0.36)	0.04 (0.16)	0.250
Ventricular couplets (%)	Baseline	3.08%	2.94%	1.0
	Week 1	3.08%	5.88%	0.68
	Week 2	3.08%	8.82%	0.27
	Week 4	13.85%	4.41%	0.07
	WLS	Time×group interaction: $P=0.061$		
Runs ventricular events (%)	Baseline	0.00%	2.26%	0.237
	Week 1	3.08%	0.00%	0.237
	Week 2	1.54%	2.94%	1.000
	Week 4	1.54%	0.00%	0.489
Multifocal ventricular events (%)	Baseline	33%	25%	0.288
	Week 1	27%	19%	0.263
	Week 2	27%	29%	0.784
	Week 4	35%	25%	0.213
	WLS	Time×group interaction: $P=0.369$		
Bradycardia (%)	Baseline	83%	92%	0.101
	Week 1	83%	72%	0.216
	Week 2	89%	78%	0.103
	Week 4	83%	80%	0.681
	WLS	Time×group interaction: $P=0.024$		
Tachycardia (%)	Baseline	97%	100%	0.151
	Week 1	100%	100%	
	Week 2	100%	98%	0.319
	Week 4	100%	100%	

Pulse analyzed by ANOVA followed by pair-wise t-tests of baseline and 6 month values and change from baseline at 6 months, with alpha set at 0.05.
Ventricular events reported as median (inter-quartile range); analyzed by Wilcoxon/Mann–Whitney non-parametric test.
Ventricular couplets, MFVEs, bradycardia and tachycardia reported as percentage of subjects, analyzed by WLS.
Runs of ventricular events and tachycardia reported as percentage (WLS not permitted because of 0 values).

of glucose was due to a significant increase in the placebo group (3 ± 9 mg/dl, $P = 0.02$).

As with the LOCF analyses, analysis of changes in serum levels of blood lipids and glucose of all subjects for whom there was complete data found significant differences for P *vs* H for LDL-cholesterol (-0.8 ± 24.2 *vs* -12.9 ± 23.1 mg/dl, $P = 0.026$), HDL-cholesterol (-0.5 ± 9.4 *vs* 4.4 ± 6.6 mg/dl, $P = 0.011$) and glucose (5.3 ± 12.1 *vs* -0.8 ± 12.8 mg/dl, $P = 0.036$; data not shown). Differences between groups for changes in serum triglycerides and total cholesterol were not significantly different ($P > 0.05$).

There were no significant changes or differences between the two groups at any time point for serum levels of any of the electrolytes measured, or for ALT, AST, or creatinine (data not shown).

Symptoms. Analysis of self-reported symptoms is shown in Table 6. The symptoms that subjects reported to be most consistently increased by the herbal *vs* the placebo treatment were dry mouth, heartburn and insomnia. These three symptoms were significantly different at each time point after baseline. Both dizziness and difficulty concentrating were higher in the herbal treatment group than the placebo group prior to treatment and these differences persisted at week 4 and month 3 for difficulty concentrating, but ceased to be different after week 4 for dizziness. Placebo subjects

Table 5 LOCF analysis of blood chemistries[a]

		Group				
		Placebo $X \pm$ s.d. (P-value)[b]		Herbal $X \pm$ s.d. (P-value)[b]		
Measure	Study period	mmol/l	mg/dl	mmol/l	mg/dl	P[c]
Total cholesterol	Baseline	5.34±1.22	211±48	5.11±1.04	202±41	0.203
	Final	5.27±1.22	208±48	4.94±0.96	195±38	0.082
	Change	−0.07±0.53	−3±21 (0.23)	−0.17±0.58	−6±23 (0.03)	0.404
LDL-cholesterol	Baseline	3.49±1.06	138±42	3.24±0.86	128±34	0.132
	Final	3.49±1.06	138±42	3.04±0.84	120±33	0.007
	Change	0±0.43	0±17 (0.84)	−0.24±0.51	−8±20 (0.0007)	0.013
HDL-cholesterol	Baseline	1.3±0.4	52±14	1.3±0.4	51±16	0.841
	Final	1.3±0.3	51±13	1.4±0.4	54±16	0.278
	Change	0±0.18	0±7 (0.73)	0.1±0.2	3±6 (0.0001)	0.004
Triglycerides	Baseline	2.93±2.03	116±80	3.11±2.63	123±104	0.650
	Final	2.73±1.67	108±66	2.78±2.66	110±105	0.890
	Change	−0.20±1.14	−7±48 (0.20)	−0.33±1.04	−12±41 (0.01)	0.515
Glucose	Baseline	5.0±0.7	91±12	5.0±0.7	90±12	0.592
	Final	5.2±0.4	94±16	4.9±0.5	89±9	0.056
	Change	0.2±0.5	3±9 (0.02)	−0.1±0.6	0±10 (0.68)	0.051

[a]Treatment was a herbal supplement containing 90 mg ephedra and 192 mg caffeine/day.
[b]P-values for within group change from baseline compared by paired samples, two-sided t-tests.
[c]Mean values of subjects in treatment ($n = 70$) *vs* placebo ($n = 69$) groups compared by ANOVA analysis, followed by pairwise t-tests of baseline and final values and changes from baseline, with alpha set at 0.05.

Table 6 LOCF analysis of self-reported symptoms

	Symptom								
	Acute phase					Chronic phase			
	B	W1	W2	W3	W4	B	M1	M3	M6
Constipation	—	H > P**	H > P**	H > P**	—	—	—	—	—
Diarrhea	—	—	—	—	—	—	—	P > H*	P > H*
Difficulty concentrating	H > P*	—	—	—	H > P*	H > P*	—	H > P*	—
Dizziness	H > P*	H > P*	H > P*	—	H > P*	—	—	—	—
Dry mouth	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Heartburn	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P*
Insomnia	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Anxiety	—	H > P*	—	—	—	—	—	—	—
Upset stomach	—	H > P*	H > P*	—	—				

Acute phase: B, baseline (prior to treatment); W1, W2, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n = 69$) or placebo (P, $n = 68$).
Chronic phase: B, baseline (prior to treatment); M1, M3, M6, months 1, 3 and 6 after treatment with either herbal (H, $n = 66$) or placebo (P, $n = 70$).
*$P < 0.05$; **$P < 0.01$ (repeated measures ANOVA of group by time interaction, followed by pair-wise t-tests).
There were no differences between treatment groups at any time point for blurred vision, chest pain, headache, irritability, nausea or palpitations.

reported more diarrhea than herbal subjects at both 3 and 6 month time points. There were no significant differences between treatment groups in self-reported chest pain, palpitations, blurred vision, headache, nausea or irritability at any time point (not shown).

Adverse effects. Reasons for withdrawal from the study are presented in Table 7. The largest reason in each group was subject choice (P, 24; H, 14). This category included subjects who did not want to continue, moved away or had changes in jobs or personal lives that reduced available time. Investigators removed seven subjects from each group for protocol violations (previously undisclosed ineligibility or noncompliance). Fifteen subjects (eight P, seven H) were asked to withdraw from the study for potential adverse effects. These included one subject who had gallbladder surgery (P) and one with elevated serum creatinine (H). All other investigator-requested withdrawals were for cardiovascular symptoms: elevated blood pressure (three P, two H), irregular heartbeat (one P, one H), MFVE (one P, one H), ventricular events (one P, one H), and ventricular runs of five or more (one P, one H). Four additional subjects withdrew from each group for self-reported cardiovascular symptoms—chest pain (two P, none H), 'loud heart beat' (none P, one H) and palpitations (two P, three H). Subjects also voluntarily withdrew for self-reported CNS effects (two P, five H), and other GI effects (one P, four H). The numbers of subjects who withdrew from the study did not differ ($P > 0.05$) between treatment groups for any individual reason or for any of the system categories.

Table 7 Reasons for withdrawal from study by randomized subjects

	Number withdrawing		
Reason for withdrawal	*Placebo (n = 43, 51%)*	*Herbal (n = 37, 44%)*	*P-value* 0.44
Subject choice	24	14	0.12
Protocol violation	**4**	**4**	**1.0**
Noncompliance	**3**	**3**	**1.0**
Cardiovascular			
Chest pain	2	0	0.50
Loud heart beat	0	1	0.46
Palpitations	2	3	0.66
Elevated blood pressure	**3**	**2**	**1.0**
Irregular heart beat	**1**	**1**	**1.0**
Multifocal ventricular event	**1**	**1**	**1.0**
Ventricular event	**1**	**1**	**1.0**
Ventricular runs of five or more	**1**	**1**	**1.0**
Total	11	10	0.80
Central nervous system			
Anxiety	0	1	0.46
Disorientation	1	0	1.0
Dizziness	1	0	1.0
Insomnia	0	2	0.21
Irritability	0	2	0.21
Total	2	5	0.24
Gastrointestinal			
Bad taste	1	1	1.0
Dry mouth	0	1	0.46
Gastroesophogeal reflux disorder	0	1	0.46
Nausea	0	1	0.46
Gallbladder removal	**1**	**0**	**1.0**
Total	2	4	0.41
Other			
Elevated creatinine	**0**	**1**	**0.46**

Total number of subjects randomized: 84 to placebo, 83 to herbal supplement (90 mg/day ephedrine and 192 mg/day caffeine). Numbers do not sum to total ns due to multiple reasons for withdrawal by some subjects. Roman type indicates subject choice or subject self-reported reason for withdrawal. Bold type indicates choice for withdrawal was made by medical and/or research staff.

Discussion

In this study, a herbal preparation containing ephedra alkaloids (from Ma Huang) and caffeine (from Kola nut), administered with diet and exercise counseling for a 6 month period, promoted significantly greater reductions in body weight, body fat and waist and hip circumferences in overweight subjects compared with similarly counseled placebo-treated subjects. Other beneficial effects that accompanied the greater weight loss of the herbal treatment group included decreased serum LDL-cholesterol, increased HDL-cholesterol levels and decreased blood glucose. These beneficial responses observed in actively treated subjects were accompanied by small persistent increases in heart rate (4 ± 9 bpm by office visit and 1 ± 7 bpm by Holter monitor). Small increases in blood pressure (≥ 3 mmHg) were also detected by 24 h ambulatory blood pressure monitor, although not by office assessment. The numbers of subjects removed from the study for potential treatment-related adverse events were similar in the herbal and placebo groups. Self-reported symptoms that were increased in the herbal treatment group were dry mouth, heartburn and insomnia. There was no difference between groups in self-reporting of palpitations or chest pain at any time point.

Body composition-related effects

The increased weight reduction with the Ma Huang/Kola nut combination in the present study is consistent with results from two previous 8 week studies of Ma Huang formulations.[11,12] These results are also consistent with those from studies of synthetic ephedrine/caffeine combinations in animals[16,17] and humans.[6,9,18] Increased weight loss with ephedrine/caffeine combination is attributed to both decreased food intake[19,20] and increased energy expenditure.[17,20]

As in the two 8 week studies, the reductions in body fat, waist and hip circumferences and the favorable changes in serum HDL and LDL cholesterol levels are probable consequences of the greater reductions in body weight in the subjects treated with the Ma Huang/caffeine combinations. It has been suggested, however, that ephedrine/caffeine combinations have specific effects to increase lipolysis and improve blood lipid profile.[21,22]

The greater body weight loss seen in the herbal treatment group here was probably also responsible for the reduction in blood glucose levels in this group *vs* placebo subjects, although this difference was not seen in a previous 8 week study.[11] Several differences between the studies could account for this, including differences in the ephedra/caffeine ratio (70/240 *vs* 90/192 mg/day), in the herbal formulations and in study length (8 weeks *vs* 6 months). Another possibility is that subjects in the present study were more careful to refrain from taking their herbal supplements prior to blood sampling, thus avoiding influence of a possible acute increase in blood glucose in the group taking the ephedra/caffeine combination.[23]

Cardiovascular effects

The effect of herbal ephedrine/caffeine combinations on blood pressure appears to be small, with previous reports of either no increase[12] or small, transitory increases.[11] As discussed elsewhere,[11] these effects on blood pressure are less than those reported with sibutramine treatment.[24] In the present study, no significant change in blood pressure was detected by office evaluation. The only statistically significant increases that were revealed with 24 h monitoring were small ($\leq$3 mmHg) and some blood pressure measures were found to be significantly decreased ($\leq$5 mmHg). Similar acute[19] and transitory[9] increases in blood pressure have been previously described with synthetic ephedrine/caffeine treatment.

The small increases in heart rate of herbally treated subjects in this study are similar in magnitude (4$\pm$9 bpm) to those observed in the previous 8 week study[11] and to those reported following acute treatment with Ma Huang,[25] or with ephedrine/caffeine.[20] Increased heart rate is consistent with the known effect of this combination to stimulate energy expenditure.[20,26] Chronic treatments with ephedrine/caffeine have been reported to have either no significant effect on heart rate[9] or a slower rate of decrease subsequent to weight loss than seen in placebo-treated subjects.[23]

Despite the small statistically significant increases in heart rate observed in this study, there were no significant increases subsequent to herbal treatment in any of the cardiac arrhythmias assessed. The decrease in incidents of bradycardia with ephedra/caffeine is related to the demonstrated effect of this combination to increase heart rate. Although there has been speculation of a link between consumption of low levels of ephedra alkaloids and arrhythmias,[2] the finding of no cause and effect relationship in the present placebo-controlled study is consistent with the lack of any research data linking synthetic ephedrine to cardiac arrhythmias.[27]

Adverse effects

There were no significant adverse effects resulting from treatment with herbal ephedra/caffeine in the present study. Some subjects were asked to withdraw and some withdrew themselves from this double-blind study for potential treatment-related side effects. Analysis upon completion of the study, however, revealed that the distribution of these subjects was almost identical between the treatment and placebo groups.

How can the absence of treatment-related adverse events in this and two previous clinical trials of ephedra combinations (334 subjects in total) be reconciled with the adverse event reports collected by the FDA from users of these products? Possible explanations include coincidence, pre-existing pathology, non-recommended usage and increased individual sensitivity.

In a FDA-sponsored analysis, Haller and Benowitz categorized 140 adverse-event reports based on how likely they believed the reported events to have resulted from the use of ephedra supplements.[2] The difficulty in making such judgements is illustrated by the controversy regarding their conclusions.[28,29] With millions of Americans consuming ephedra-containing products, it is obvious that some number of adverse events is expected each year regardless of consumption of these products. The real question is not whether adverse events occur in a population undergoing treatment, but whether these occur at a rate that is higher than that of a matched, untreated group. This is impossible to determine from adverse event reports alone. The randomized, placebo-controlled trial allows evaluation of cause and effect relationships *vs* coincidental events.

Most clinical trials purposely exclude individuals with pre-existing medical conditions to avoid confounding of results. It is therefore not justified to extrapolate results from such trials to individuals with such exclusionary medical conditions or to extrapolate results beyond amounts or time periods that have been studied. The possibility of unfavorable interactions between herbal combinations and other medications, either prescription or illicit, should be recognized and warning labels present on herbal products should be adhered to.

Some have expressed the theory that adverse event reports may reflect an unusually high degree of sensitivity in a small fraction of individuals.[2,25] Because of the low suspected incidence, this type of sensitivity might not be revealed in a clinical trial, but requires a case–control study of a very large number of individuals.[25] Such a study would be difficult to conduct, but may be the only way to address the question of rare hypersensitivity.

Conclusion

The present study demonstrated significant beneficial effects on body weight, body fat and blood lipids of a herbal Ma Huang/Kola nut mixture (90/192 mg/day ephedrine alkaloids/caffeine) in overweight men and women who were otherwise healthy. Compared with placebo, the tested product produced no adverse events and minimal side effects that are consistent with the known mechanisms of action of

ephedrine and caffeine. Extrapolation of the present findings to usage by individuals with medical complications (diabetes, heart disease, etc) is unwarranted and usage by such individuals is contra-indicated on labels of commercial products. Evidence from three completed placebo-controlled clinical trials of herbal ephedra/caffeine is consistent with that from a large number of studies with synthetic ephedrine/caffeine. In total, these suggest that herbal ephedra/caffeine herbal supplements, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events. The current widespread usage of herbal products and the increasing incidence of obesity warrant additional clinical trials to confirm and extend these results.

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Appendix I: medical exclusions from the study

Active heart disease, a positive history of palpitations, hypertension (office measurement ≥ 140 systolic BP or diastolic BP ≥ 90 or ABPM mean 24 h systolic BP ≥ 139 mmHg or diastolic BP ≥ 87 mmHg), epilepsy, history of mental illness, hyperthyroidism, chronic use of any drug (by self-report or by presence in urine toxicology screen) except oral contraceptives, hormone replacement therapy or synthetic thyroid hormone, active bulimia, known prostatic hypertrophy, pregnancy (reported or detected by HCG testing), glaucoma, active cancer or cancer in remission for ≤ 5 y, renal dysfunction, liver dysfunction (ALT, alkaline phosphatase $> 2\times$upper limit of normal), acute or chronic active hepatitis, AIDS, any acute illness within the past 4 weeks, any other chronic illness that might be adversely impacted by concurrent use of the herbal compound, concurrent participation in another research protocol involving diet or any drug use, concurrent participation in a diet program involving severe calorie restriction (800 or fewer calories per day), caffeine intake of 500 mg per day or greater, use of appetite suppressant drugs or ephedra-containing herbal supplements within the last 6 months and weight change of 5 kg or more within the past 3 months.

Appendix II: urine toxicology screen

Amphetamine metabolites, salicylates, phenothiazines, amphetamine class, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, tricyclics, methanol, ethanol, acetone, iso-propanol, ethchlorvynol.

Prepared Statement of the Federal Trade Commission

J. Howard Beales, III
Director, Bureau of Consumer Protection

Mr. Chairman and members of the Subcommittee, I am Howard Beales, Director of the Bureau of Consumer Protection, Federal Trade Commission ("FTC" or "Commission"). The Commission is pleased to have this opportunity to provide information concerning our efforts to ensure the truthfulness and accuracy of marketing for dietary supplements, including weight loss products and other supplements containing the herbal ingredient, ephedra.[1] I will discuss the Commission's mission, our latest activities in the weight-loss area, and then address the specific questions you raised.

The mission of the Federal Trade Commission is to prevent unfair competition and to protect consumers from unfair or deceptive practices in the marketplace. As part of this mission, the Commission has a longstanding and active program to combat fraudulent and deceptive advertising claims about either the health benefits or safety of dietary supplements.[2] The dietary supplement industry represents a substantial and growing segment of the consumer healthcare market. Industry sales for 2001 were estimated to be $17.7 billion.[3] The supplement category encompasses a broad range of products, from vitamins and minerals to herbals and hormones.

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[1] The written statement presents the views of the Federal Trade Commission. Oral testimony and responses to questions reflect my views and do not necessarily reflect the views of the Commission or any Commissioner.

[2] Our authority in this area derives from Section 5 of the Federal Trade Commission Act, which prohibits "unfair or deceptive acts and practices in or affecting commerce," and Section 12, which prohibits the false advertisement of "food, drugs, devices, services or cosmetics." 15 U.S.C. §§ 45, 52.

[3] Source: *Nutrition Business Journal*, Supplement Business Report 2002.

There is no question that some of these products offer the potential for real health benefits to consumers. The scientific research on the associations between supplements and health is accumulating rapidly. Unfortunately, unfounded or exaggerated claims in the marketplace have also proliferated. The role of the Federal Trade Commission is to ensure that products are marketed in a manner that is truthful and not misleading, and that consumers have adequate information about the efficacy and safety of dietary supplements to make well-informed decisions. The Commission attempts to accomplish this goal through its law enforcement efforts and consumer and business education.

Today the Commission's testimony will provide an overview of our enforcement efforts and other activities to combat deception in the supplement marketplace. The Commission's testimony will focus on our activities to combat the false and unsubstantiated claims being made in the weight loss product category.

The FTC's Dietary Supplement Advertising Program

Challenging misleading or unsubstantiated claims in the advertisement of dietary supplements is a priority of the FTC's consumer protection agenda. The Commission has filed more than 80 law enforcement actions over the past decade challenging false or unsubstantiated claims about the efficacy or safety of a wide variety of supplements. The Commission focuses our enforcement priorities on national advertising claims for products with unproven benefits, products promoted via the Internet and elsewhere to treat or cure serious diseases, and claims for products that present significant safety concerns to consumers.

As in all our advertising programs, we work to make sure our enforcement actions have a strong impact. For example, the Commission holds accountable not just the supplement manufacturer but other parties that play a role in deceptive marketing, like ad agencies, infomercial producers, distributors, retailers, catalog companies, and celebrity endorsers.[4] In addition, we have sought to obtain more meaningful relief for consumers, going beyond the basic cease and desist orders in many cases, to require substantial monetary relief for consumer redress or disgorgement of profits.[5] Finally, when the marketing of a supplement raises safety concerns, the Commission has required that strong warning statements be placed in labeling and advertising.[6]

Weight Loss Advertising Report

As the Subcommittee is aware, ephedra is often marketed as a weight-loss product. Last month, the staff of the Federal Trade Commission released a "Report on Weight-Loss Advertising: An Analysis of Current Trends."[7] The report was initiated as a response to increasing recognition of the detrimental effects of obesity and to the serious challenges facing

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[4] *See, e.g., Steven Patrick Garvey, et al.* 00-09358-AHM(AIJx)(C.D. Cal. Nov. 15, 2000) (pending litigation against celebrity endorser for "Fat Trapper" infomercial).

[5] *See, e.g., Enforma Natural Prods., Inc.,* 04376JSL (CWx)(C.D.Cal. April 25, 2000)(Stipulated Final Order including $10 million in consumer redress); *Slim America, Inc.,* 97-6072-CIV-Ferguson (S.D. Fla. June 30 1999)(Final judgment for permanent injunction and damages, including $8.3 million in consumer redress).

[6] *See* discussion of Question 1 *infra*.

[7] "Weight-Loss Advertising: An Analysis of Current Trends" A Federal Trade Commission Staff Report (Sept. 2002) ("Weight Loss Advertising Report"). Copies of the report are available on the Commission's web site, www.ftc.gov.

law enforcement agencies in their efforts to stop deceptive advertising for weight loss products and services. Consumers spend billions of dollars on products that purport to promote weight loss. A majority of these products appear to fall into the dietary supplement category.[8]

The FTC staff's Weight Loss Advertising Report analyzed claims from a nonrandom sample of 300 advertisements disseminated during the first half of 2001, including ads in all major forms of media. With the assistance of members of the Partnership for Healthy Weight Management, the staff collected ads from television, direct mail, and the Internet. Staff also obtained a sample of ads from newspapers and conducted a more systematic review of ads appearing in selected magazines. By comparing a sample of ads disseminated in 1992 and 2001 in eight national magazines, the Commission staff looked at trends in the frequency of ads, the types of products marketed, and the most common advertising techniques. The analysis showed that more than half (55%) of the ads collected contained at least one representation that was very likely to be false or to lack substantiation. The historical comparison of magazine ads also revealed a much higher frequency of questionable claims and marketing techniques in 2001 compared to a decade ago. For example, ads in the 2001 magazine sample were much more likely to use dramatic before-and-after photos and other consumer testimonials, to promise substantial, rapid and permanent weight loss, often without any diet or exercise, and to promise "guaranteed" and "scientifically proven" results.

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[8] A historical comparison of ads appearing in a sample of eight national magazines in both 1992 and 2001 found that two-thirds of the products promoted in the 2001 sample were for dietary supplements, representing a major shift from 1992 when meal replacement products were the most promoted category. Weight Loss Advertising Report at 21.

Public Workshop on Weight Loss Products

In light of the findings of the Weight Loss Advertising Report the Commission will explore other strategies, beyond traditional law enforcement efforts, to curb deception in the weight loss industry. Even with an increase in enforcement actions by the FTC and other agencies in the past decade, deceptive claims continue to rise.[9] Aggressive law enforcement will always remain a critical component of an effective program to combat weight loss scams, but it is clear that we must also pursue other approaches. The Commission will continue to engage in consumer education efforts to increase awareness of weight loss scams and will work with industry toward better self-regulatory programs.

Toward that end, the Commission is holding a public workshop on Advertising of Weight Loss Products on November 19.[10] The purpose of the workshop is to explore both the impact of deceptive ads on the public health and new approaches to fighting the proliferation of misleading claims. A wide variety of stakeholders, including government officials, scientists, public health groups, marketers of weight loss products, advertising professionals, and representatives of media have been invited to participate.

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[9] The FTC has filed more than 80 cases in the past ten years against deceptive weight loss advertising for supplements and other products and services – as many actions as in the prior seven decades combined.

[10] *See* Public Workshop: Advertising of Weight Loss Products, 67 Fed. Reg. 59,289 (Sept. 20, 2002).

With that background about the FTC's dietary supplement program and our activities relating to weight loss advertising, the testimony will now focus on the specific questions posed by the Subcommittee.

1. Please discuss the enforcement actions that FTC has taken against companies that have marketed ephedra-containing products as safe and without side effects.

The FTC has brought four enforcement actions challenging unqualified safety/no side effects claims for supplements containing ephedra.[11] These actions have included products marketed as alternatives to street drugs such as Ecstacy as well as body-building supplements and energy supplements. FTC staff also has additional non-public investigations pending that include safety claims for ephedra products. Although we recognize that the Department of Health and Human Services (HHS) is awaiting the completion of a review of the scientific evidence on ephedra safety, under the FTC Act an advertiser is required to have competent and reliable scientific evidence supporting claims made in advertising before they are made. Under that standard, the FTC has alleged that unqualified safety claims in advertising for ephedra products are deceptive.

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[11] *Robert C. and Lisa M. Spencer, dba Aaron Co.,* C-4019 (July 30, 2001)(Consent Order involving safety claims for an energy product containing ephedra); *AST Nutritional Concepts and Research, Inc., et al.*, Civ. No. 99-WY-2197 (D. Co. May 4, 2000)(Stipulated Final Order involving safety claims for body-building supplements containing both androstenedione and ephedra); *Mex-RX US, Inc., et al.*, Civ. No. SACV99-1407-DOC(ANX)(C.D. Cal. Nov. 24, 1999)(Stipulated Final Order involving safety claims for body-building supplements containing both androstenedione and ephedra); *Global World Media Corp.,* C-3772 (Oct. 9, 1997)(Consent Order involving street drug alternatives containing ephedra).

In each of the four ephedra cases, the Commission has imposed orders that both prohibit unsubstantiated safety claims and require a strong disclosure warning about safety risks in all future advertising and labeling by the respondent.[12] In addition, the order against Global World Media Corp., for its marketing of ephedra as a street drug alternative, includes a prohibition against marketing in media targeted at young audiences.[13]

2. Does the FTC believe that ephedra-containing products are safe? Would such a claim be substantiated by current science? What percentage of advertisements for ephedra products claimed that they were safe? What percentage of ephedra ads included warnings about the health risks associated with the use of the product?

The FTC act requires that objective claims about products and services be substantiated

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[12] For example the consent order in *Robert C. Spencer and Lisa M. Spencer, supra,* n. 11, requires that the following statement be included in all advertising, labeling and other marketing of ephedra products:

> **WARNING:** This product contains ephedra or ephedrine alkaloids, which can have dangerous effects on the central nervous system and heart and can result in serious injury. Risk of injury can increase with dose, and may even include heart attack, stroke, seizure or death. Consult a health care provider prior to use if you have high blood pressure, heart or thyroid disease, diabetes, difficulty urinating, prostate enlargement, or glaucoma, or are using any prescription drug. Do not use if you are taking a MAO inhibitor or any allergy, asthma, or cold medication containing ephedrine, pseudoephedrine or phenylpropanalomine. Discontinue use if you experience rapid heart beat, chest pain, severe headache, shortness of breath, dizziness, sleeplessness or nausea. This product is not recommended for use if you are or could be pregnant unless a qualified health provider tells you to use it. The product may not be safe for your developing baby.

A shorter version of this statement is required for television and radio advertisements. The FTC staff coordinated closely with FDA staff in developing this warning to ensure that it was consistent with FDA's current assessment of the safety concerns.

[13] Specifically, the consent order prohibits disseminating any ads for Herbal Ecstacy and similar products containing ephedra in any media where more than 50% of the audience is under 21 years of age. *Global World Media Corp., supra,* n.11.

before the ad is disseminated. The substantiation standard required for safety claims is one of "competent and reliable scientific evidence." As discussed in response to Question 1, the FTC has brought four cases alleging that unqualified safety claims for ephedra are not substantiated by this level of evidence and thus violate Section 5 of the FTC Act.[14]

Twenty-three ads, or about 8%, of the 300 sampled for the Weight Loss Advertising Report identified ephedra, ephedrine or Ma Huang as an ingredient.[15] Of these:

- 11, or 48%, made safety claims.[16]
- 7, or 30%, included a specific health warning about ephedra's potential adverse effects.

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[14] In addition to the ephedra cases, the Commission has also challenged, as unsubstantiated or false, safety claims for other dietary supplement ingredients including for: 1) cure-all remedies containing comfrey, a botanical ingredient that has been associated with severe liver toxicity, *see, e.g., Christopher Enterprises, Inc., et al.*, 2:01 CV-0505 ST (C.D. Utah Nov. 29, 2001)(Stipulated Final Order); 2) body-building supplements containing androstenedione, a steroid hormone that is linked to potentially dangerous changes in estrogen and testosterone levels in the body, *see, e.g., Met-RX USA, Inc.* and *AST Nutritional, supra,* n.11; and 3) HIV/AIDS treatments containing St. John's wort, a botanical that has been found to interfere with certain medications, including those used to treat HIV/AIDS, *see, e.g., Panda Herbal International, Inc.* et al. C-4018 (July 30, 2001)(Consent order).

When the Commission files a complaint, it alleges that it has "reason to believe" that the practices cited in the complaint violate the FTC Act. A consent order that is reached in settlement of such allegations does not constitute an admission by the respondent that a law violation has occurred.

[15] There are a number of other ads that did not disclose ephedra as an ingredient but that the Commission knows include the ingredient. In addition, 60% of the sampled ads that made safety claims did not identify ingredients at all, so it is not possible to determine the total percentage of sampled ads making safety claims for ephedra weight loss products.

[16] Of the sampled ads containing ephedra that made safety claims, 55% also contained a specific health warning.

3. The FTC's recent report about the increased number of deceptive advertisements for weight loss products compared advertisements in 1992 and 2001. Please explain the rationale for choosing the year 1992 for this analysis.

The year 1992 was selected for comparison because it allowed staff to compare ads that appeared after the FDA promulgated its final rule on weight loss products with ads appearing after the 1994 passage of the Dietary Supplement Health and Education Act (DSHEA).[17]

4. Certain products require pre-market approval prior to sale in the United States. Dietary supplements do not require such pre-market approval. Therefore, the public may experience considerable exposure to an unsafe dietary supplement before any government action ensues. Is the FTC the most appropriate agency to be policing the safety of dietary supplements?

The Food and Drug Administration has both the expertise and the principal statutory authority to oversee the safety of dietary supplements. The Federal Trade Commission also gives enforcement priority to cases involving false or unsubstantiated safety claims in supplement advertising and by engaging in education efforts to alert consumers to potential safety risks. Our efforts are coordinated closely with FDA staff and we rely heavily on FDA and other scientific agencies for advice on the health effects of supplements. We view our activities on supplement safety as playing an important supporting role to FDA's more comprehensive efforts to ensure the safety of dietary supplements.

5. Since passage of the Dietary Supplement Health and Education Act, FTC enforcement

[17] *See* Weight Loss Advertising Report at 21.

against deceptive marketing of products has increased significantly, with FTC law enforcement cases involving weight loss products or services in the nineties equaling those filed in the previous seven decades. Does this indicate that the elimination of the requirement for pre-market approval by the FDA has left consumers only protected by the FTC?

The comparative analysis of magazine advertising from 1992 and 2001 indicates that there has been an increase both in the overall volume of ads for weight loss products and services and in the incidence of deceptive or misleading claims.[18] In response, the FTC has stepped up both its own enforcement efforts and its efforts to coordinate with other law enforcement authorities. The Federal Trade Commission is not the only agency to police the dietary supplement industry. DSHEA requires a manufacturer of a dietary supplement to have substantiation for any structure/function claims so that the claim is truthful and not misleading. We, therefore, coordinate our enforcement efforts closely with the Food and Drug Administration. In addition, we work closely with the state Attorneys General, and other state and local law enforcement authorities. We are also increasing our efforts to combat cross border fraud in the weight loss industry and other health-related industries by coordinating with law enforcement agencies in Canada, Mexico and other countries.

6. Would the FTC agree that it is inefficient to have to screen product marketing once it is on the market rather than before it goes to market? Would the system be more efficient if FDA were allowed to screen the claims made by dietary supplement manufacturers based on current scientific knowledge?

At this time, the Commission is not aware of any systematic analysis of the relative efficiency of preclearance versus post-claim enforcement in the dietary supplement market. The

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[18] *See* Weight Loss Advertising Report at 21-24.

FTC does not pre-screen advertising claims for dietary supplements or any other product or service within its jurisdiction. Instead, the agency addresses deception in the marketplace largely through post-market enforcement actions targeted against specific false or misleading claims. In applying this approach, the agency seeks to balance the risk of allowing commercial speech that might prove to be false or misleading and the risk of banning or delaying commercial speech that might prove to be true. Considerations like the nature of the claims and the risks that may result from deception are important components of this balancing. Claims about health and safety, in particular, require a rigorous substantiation standard as well as a strong and active enforcement program to back up that standard. The Commission's role in reviewing the truthfulness and accuracy of claims presumes that products are legally in the marketplace and do not pose an unacceptable risk of consumer injury.

7. Against what percentage of bad actors does FTC have the resources to take enforcement action? Does this leave a large number of bad actors continuing to market to an unsuspecting public because the FTC only has the resources to go after the most prominent and egregious actors?

Although there is no definitive data to respond to your specific question, the weight loss advertising report strongly suggests that the incidence of false and deceptive claims has increased over the past decade. The Commission has made enforcement against deceptive supplement advertising, including weight loss supplements, a priority of its consumer protection mission and devotes significant resources to investigation and prosecution of cases against false and unsubstantiated advertising in this industry. As in any law enforcement effort, the Commission attempts to direct its resources to the cases involving the greatest amount of harm or otherwise

serving an important law enforcement interest. It is important that we continually reassess the efficacy of our enforcement efforts and examine alternative approaches that may increase our effectiveness. These are the questions that we will be examining at our November 19 workshop on weight loss advertising.

Aggressive law enforcement is a critical component of an effective program to combat market deception. At the same time, it seems clear that we should pursue other strategies like consumer education, better industry self-regulation, and encouraging better media screening of facially false ads. Our workshop will focus on ways to enhance our current approaches to curbing deceptive weight loss advertising and on coming up with creative new strategies to maximize the efficient use of our law enforcement resources.

Conclusion

The Commission thanks this Subcommittee for focusing attention on this important consumer health issue and for giving the Federal Trade Commission an opportunity to discuss its role. The Commission looks forward to working with the Subcommittee on initiatives concerning our dietary supplement program and our activities involving weight loss marketing.

Testimony of
Bill Jeffery, L.LB.,
Centre for Science in the Public Interest (Canada)
National Coordinator

Good morning. I am Bill Jeffery, National Coordinator of the Centre for Science in the Public Interest (CSPI) for Canada. CSPI is an independent health advocacy organization, focussing on nutrition and food safety, with offices in Ottawa, Canada and Washington, D.C. CSPI's Canadian advocacy efforts are supported by 125,000 subscribers to the Canadian edition of its *Nutrition Action Healthletter*. CSPI does not accept funding from either industry or government.

I am pleased to have the opportunity today to address the issue of how ephedra and other dietary supplements (or what we call in Canada "natural health products") should be regulated. I was specifically asked to address the following seven questions. I have provided complete answers to these questions in my prepared statement and I request that they be incorporated into the record.

1. Please discuss the reasons that Health Canada withdrew many ephedra-containing dietary supplements from the market.

Following two prior public advisories concerning health risks associated with unapproved products containing ephedra/ephedrine, Health Canada conducted a risk assessment and determined that, on the basis of at least 60 adverse reaction reports and one death in Canada (and similar international evidence), these products constituted a Class 1 health risk for some vulnerable population groups.[1] A Class 1 health risk is "a situation where there is a reasonable probability that the use of, or exposure to, a product will cause serious adverse health consequences or death." Accordingly, Health Canada issued a voluntary recall of the offending products on January 8, 2002.

2. Did your organization support Health Canada's decision?

We support the recall of ephedra-containing products because the small benefit of taking ephedra to lose weight (about one or two additional pounds lost per month for up to four months) is not worth the risk of stroke, cerebral haemorrhage, heart attack, and death. Experts may quibble over individual reports of adverse reactions, but it is beyond dispute that ephedra triggered many serious complications and deaths in the United States and Canada.

3. Did many other consumer and health advocacy groups support Health Canada's decision?

At least nine organizations issued notices of Health Canada's voluntary recall on their web-sites, including the Canadian Medical Association, the Canadian Pharmacists Association, and the National Association of Pharmacy Regulatory Authorities.[2] At least three other organizations publicly criticised Health Canada for not taking even stronger steps to prevent the sale of ephedra-containing products. They include the Canadian Health Coalition, the British Columbia Medical Association, and the Vancouver-based St. Paul's Hospital Eating Disorders Program.

4. Please discuss the regulatory system in Canada that oversees dietary supplements.

Currently, the Canadian *Food and Drugs Act*[3] and *Regulations* do not include a special regulatory category for herbal remedies. Accordingly, they are technically considered to be drugs and could be regulated as such.[4] Vitamin and mineral supplements are explicitly regulated as drugs in Part D of the *Regulations*. Generally, drugs must be pre-approved for sale by the Minister of Health, assigned a Drug Identification Number (D.I.N.)[5] and must bear the D.I.N. on the label when sold to the public.[6]

Until forthcoming natural health product regulations are in place, Health Canada is only taking regulatory actions against herbal remedies and other natural health products when they pose health risks or make claims about benefits in relation to 39 diseases and health conditions listed in "Schedule A" to the *Act*. The vast majority of natural health products currently on the market do not have health claims on labels.

The Federal Government pre-published proposed amendments to the *Food and Drug Regulations* on December 22, 2001 that, if approved, would establish a regulatory framework for licensing natural health products and production facilities. The proposed amendments would also set standards for Good Manufacturing Practices, quick mandatory adverse reaction reporting, and label disclosures. Under the proposed regulations, the Minister of Health would have the power to revoke product and site licenses and take other enforcement actions.[7]

The *Food and Drugs Act* does not empower the Minister to issue mandatory recalls for drugs or natural health products.[8] Health Canada's experience is that requests for recalls are almost universally respected making it virtually unnecessary to resort to more rigorous enforcement powers such as seizing products or obtaining injunctions against sale.[9]

5. Has Health Canada taken other actions to safeguard Canadians from dangerous dietary supplements?

Health Canada issued a voluntary recall and stop-sale directive for products containing the herb Kava on August 21, 2002[10] after receiving reports of four cases of non-fatal liver toxicity in Canada. On June 19, 2002, a voluntary recall was issued concerning seven herbal supplements: Arthrin, Osporo, Poena, Neutralis, Oa Plus, Ra Spes and Hepastat found to contain undisclosed pharmaceutical drugs. Since November 1999, Health Canada issued at least 10 other voluntary recalls involving 31 natural health products[11] and several other public advisories concerning products causing adverse interactions with prescription drugs and products that were seized or turned back at ports of entry.

6. Does the fact that these products are so widely available here in the United States pose a risk for Canadian consumers?

According to Health Canada, these types of products are frequently imported from the US for personal use, or to be sold clandestinely in fitness centres, truck stops (to improve wakefulness), and elsewhere. Canadian or American truck drivers obtaining this product during trips in the United States may pose highway traffic accident risks if they use the product while driving in Canada.

7. Are there other actions that your organization would like to see Health Canada take to better safeguard Canadians with respect to dietary supplements?

CSPI and the editor of the Canadian Medical Association Journal have voiced the concern that Health Canada is excessively reliant on guidance from the natural health products industry in developing the new regulatory program. CSPI believes that Health Canada should instead rely on a panel of experts with no conflicts of interest. Furthermore, the proposed natural health product regulations do not assure a publicly transparent system of review for product safety and efficacy. We believe that active ingredients of such products are, by definition, not subject to proprietary confidentiality (patent or otherwise) and, accordingly, their safety and efficacy is best reviewed through a fully transparent process of safety and efficacy review, prior to approval. Lastly, while voluntary recalls are typically heeded, including mandatory recall authority in the *Act*, for drugs and natural health products, would reinforce the capacity of Health Canada to protect the public health in an administratively efficient manner.

I would like to thank the Committee for the opportunity to testify and will be happy to answer any questions.

ENDNOTES

1. Such groups include persons with pre-existing conditions such as hypertension, diabetes, heart disease, etc.

2. Others include: the Ontario College of Pharmacists, the Ordes de pharmaciens du Québec, and the Calgary Health Region. At least three Canadian amateur sport organizations posted web-site notices of the recall prepared by the Canadian Centre for Ethics in Sport. (See: Judo Canada at http://www.judocanada.org/results/022202.html, Cross Country [Skiing] Canada at http://canada.x-c.com/coaching/technical/advisorynote.htm , Federation of Canadian Archers at http://www.fca.ca/weeklys/2002/8feb02.html.) See also, notices posted by the following consumer magazines: Energy Magazine at http://www.energymagazine.com/news/?news_id=2 and Natural Life Magazine at http://www.life.ca/nl/84/ephedra.html . Seven pharmaceutical and herbal manufacturers and retailers issued public statements either supporting the Health Canada recall (e.g., Beohringer Ingelheim Canada (BIC), S & H Health Foods in Kitchener, Ontario) or stressing that their products do not contain enough ephedra/ephedrine to be captured by the recall (e.g., including Pfizer Canada, BIC, Herbal Success Inc., McNeil Consumer Healthcare in relation to Tylenol); see, Canada News Wire news releases for January 10-11, 2001 at http://keyword.newswire.ca/cgi-bin/keyword.cgi?BIN=ME&QUERY=ephedrine. In addition, the following retail stores publicly stated that their products did not include items encompassed by the recall: Hy and Zel's retail store in Cambridge Ontario, and Nathuleal retail store in Kitchener, Ontario.

3. See, generally, the *Food and Drugs Act,* R.S.C. 1985, c. F-27.

4. Drug is defined in section 2 of the *Food and Drugs Act,* R.S.C. 1985, c. F-27 as:

> " includes any substance or mixture of substances manufactured, sold or represented for use in
>
> (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals,
> (b) restoring, correcting or modifying organic functions in human beings or animals, or
> (c) disinfection in premises in which food is manufactured, prepared or kept;"

5. Section C.01.014 of the *Food and Drug Regulations*, C.R.C., c. 870 states:

"Assignment and Cancellation of Drug Identification Numbers

C.01.014. (1) No manufacturer shall sell a drug in dosage form unless a drug identification number has been assigned for that drug and the assignment of the number has not been cancelled pursuant to section C.01.014.6." [The *Regulations* then prescribe the application procedure.]

6. Section C.01.005 of the *Food and Drug Regulations,* C.R.C., c. 870 states the following:

C.01.005. (1) The principal display panel of both the inner label and outer label of a drug sold in dosage form shall show in a clear and legible manner the drug identification number assigned by the Director for that drug pursuant to subsection C.01.014.2(1), preceded by the words "Drug Identification Number" or "Drogue : identification numérique" or both, or the letters "DIN".

7. See the proposed natural health products regulations in: *The Canada Gazette, Part I*, Vol. 135, No. 51 (December. 22, 2001) pp. 4912-4971 at: http://www.canada.gc.ca/gazette/hompar1-2_e.html.

8. In contrast, section 19 of the *Canadian Food Inspection Agency Act* authorizes the Minister of Agriculture and Agri-Food to issue mandatory recalls for foods. See: *Canadian Food Inspection Agency Act*, R.S.1997, c. 6.

9. Approved drugs posing health risks may be subject to mandatory stop-sale orders pursuant to subsection C.01.013(3) of the *Food and Drug Regulations*, C.R.C., c. 870.

10. See: http://www.hc-sc.gc.ca/english/protection/warnings/2002/2002_56e.htm.

11. See, for instance, http://www.hc-sc.gc.ca/english/protection/warnings/2002.htm and http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/adviss_tpd_bgtd_e.html and http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/publicat/adrv12n4_e.html#6.

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Statement

for the Record

to the

Subcommittee on Oversight of Government Management,
Restructuring and the District of Columbia
Committee on Governmental Affairs
United States Senate

RE: **Dangers of Dietary Supplement Ephedra**

Presented by: Ronald M. Davis, MD

October 8, 2002

Division of Legislative Counsel
202 789-7426

STATEMENT

for the Record

of the

American Medical Association

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RE: DANGERS OF DIETARY SUPPLEMENT EPHEDRA

October 8, 2002

Good morning Chairman Durbin and members of the Subcommittee. I am Ron Davis, MD, a member of the Board of Trustees of the American Medical Association (AMA). I am pleased to be able to testify today on behalf of the AMA. As a preventive medicine physician, I serve as director of the Center for Health Promotion and Disease Prevention at the Henry Ford Health System in Detroit, Michigan.

The physician members of the AMA are very concerned about the quality, safety, and efficacy of dietary supplement products, especially herbal (botanical) products, and we commend Chairman Durbin and this Subcommittee for their continued focus on this problem. I would like to begin this testimony with a series of questions.

- Do dietary supplement products actually contain the active ingredient(s) (and strength[s]) that their manufacturers claim on the labeling?
- Are these products really as safe as the promotional materials of the manufacturers claim them to be?
- Does the degree of safety change in individuals who have pre-existing diseases and conditions, or in those individuals who are also taking prescription medications?
- Are the structure/function claims for these products accurate and based on good science?
- Are these products being used inappropriately to treat diseases or potentially delaying individuals with diseases from obtaining effective care that may include prescription medications?

The AMA does not believe that satisfactory answers to these questions have been offered to either public health officials or the general public. Because dietary supplements are classified as foods rather than drugs, rigorous safety and efficacy standards are not required

for these products. Also, standards for product quality and for Good Manufacturing Practices (GMP) do not yet exist.

The primary obstacle to effective regulation in this area is the Dietary Supplement Health and Education Act of 1994 (DSHEA), which fails to provide for adequate Food and Drug Administration (FDA) regulatory oversight of dietary supplements. The AMA has urged Congress to amend DSHEA to require that dietary supplements, including those products already in the marketplace, undergo FDA approval for evidence of safety and efficacy; meet standards established by the United States Pharmacopoeia (USP) for identity, strength, quality, purity, packaging, and labeling; and meet FDA postmarketing requirements to report adverse events, including drug interactions.

The AMA commends the HHS Office of Inspector General (OIG) for its report entitled, "Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve," that found the current regulatory system for dietary supplements to be substantially inadequate. The AMA supports the OIG's recommendations to strengthen the standards to which dietary supplements are subject.

In the absence of modifications to the current federal law, the FDA must aggressively regulate dietary supplements to the fullest extent possible, to fulfill its obligation to protect the health of the American public. The AMA has expressed this view to the FDA on numerous occasions through letters to the Commissioner and to various FDA Dockets.

Because dietary supplements are classified as foods under federal law, they are assumed to be safe and are subject to limited regulatory oversight. Therefore, it is imperative that dietary supplement products have essentially no risks, i.e., they must be extremely safe, and provide some benefits for consumers. As discussed below, the AMA believes that dietary supplement products containing ephedrine alkaloids fail to satisfy this requirement for a high benefit/risk ratio.

As requested, the AMA has structured its statement to respond to the six questions posed by the Subcommittee.

Question 1. Why has the AMA asked the FDA to initiate proceedings to remove dietary supplement products containing ephedrine alkaloids from the United States market?

In letters dated September 28, 2000, and January 28, 2002, the AMA encouraged the FDA to initiate proceedings to remove dietary supplements containing ephedrine alkaloids from the United States market. The AMA believes the FDA has sufficient cause to take this action under Section 402(f)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Specifically, these products should be deemed adulterated because they present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling. Unfortunately, the Agency has failed to acknowledge or respond to the AMA's comments.

The AMA has taken this position based on a number of considerations:

a. Over 1,000 voluntarily submitted Adverse Event Reports (AERs) associated with dietary supplements containing ephedrine alkaloids have been received by the FDA. A number of these AERs have described events that have resulted in death or serious morbidity (e.g., cardiac arrhythmias, myocardial infarctions, seizures and strokes). Many of these AERs were for young, presumably healthy, adults. Additionally, a subset of individuals may develop drug-seeking behavior or dependence on ephedra-containing products. Due to the nature of voluntary patient safety reporting systems, these AERs underestimate the actual number of adverse events that have occurred. As noted in the Subcommittee's invitation to appear, one company alone recently admitted to having received, since 1995, more than 14,000 AERs associated with dietary supplements containing ephedrine alkaloids.

b. In August 1996, after reviewing approximately 800 AERs and other evidence, a majority of the members of FDA's Food Advisory Committee stated that, "based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements." It recommended that FDA remove dietary supplements containing ephedrine alkaloids from the market. However, the FDA did not take this advice.

c. Similarly, in 2000, four outside experts (two in clinical pharmacology and one each in psychopharmacology and neurology) commissioned by the FDA to review 140 new AERs concluded that a number of serious adverse events, including deaths, were most likely due to ephedrine alkaloids in dietary supplements. Three of these experts believed that dietary supplements containing ephedrine alkaloids posed a significant and unreasonable risk.

d. The AMA recognizes that it is difficult to prove cause-and-effect relationships based on voluntary AERs. Nonetheless, the primary question that should be considered by the FDA is whether manufacturers' claims of purported benefits for these products outweigh the products' risks. We continue to believe that the benefits do not outweigh the risks, and the weight of the available clinical evidence supports the removal of dietary supplement products containing ephedrine alkaloids from the market. Purported uses for these products include weight loss, energy enhancement, enhancement of athletic performance, body building, and euphoria. The AMA strongly believes that, with the possible exception of weight loss, the other purported uses of dietary supplements containing ephedrine alkaloids are of questionable benefit. Moreover, the AMA is unaware of any well-controlled clinical trials that prove efficacy for these purported uses. Taking into account the high number of AERs and the extremely questionable uses of ephedrine alkaloid-containing products, the AMA believes the benefit/risk ratio for these products is unacceptable.

e. Obesity is a significant public health problem in the United States. However, the AMA's position is that obesity should be categorized as a disease whose management should include dietary modification, exercise, and, when indicated, drug therapy. A number of prescription drugs, including phentermine, phendimetrazine, orlistat, and sibutramine, are available to treat obesity in the United States. In addition, surgical procedures can be used to treat morbid obesity. In Denmark, ephedrine alkaloids are

available to treat obesity, but these products can be obtained only by prescription. Interestingly, phenylpropanolamine, one of the active constituents in ephedrine alkaloids, recently was withdrawn as an over-the-counter drug for appetite suppression (also as a decongestant) from the U.S. market because it was associated with an increased risk of hemorrhagic stroke.

f. National Institutes of Health (NIH) guidelines for the treatment of obesity state that herbal preparations, including ephedra-containing products, are not recommended as part of a weight-loss program.

g. Recently, Health Canada, the Canadian agency with FDA-like authority, requested a recall of many *Ephedra*/ephedrine-containing products from the market because such products pose a serious risk to health. Specifically, Health Canada recalled:

- *ephedra*/ephedrine products with a dose unit of more than 8 mg of ephedrine, or a label recommending more than 8 mg/dose or 32 mg/day, and/or a labeled or implied use exceeding 7 days;
- all combination products containing *Ephedra*/ephedrine together with stimulants (e.g., caffeine) and other ingredients which might increase the effect of *Ephedra*/ephedrine in the body; and
- *ephedra*/ephedrine products with labeled or implied claims for appetite suppression, weight-loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects.

In conclusion, the AMA encourages the FDA to initiate proceedings to remove dietary supplements containing ephedrine alkaloids from the United States market because the risks associated with the use of these products outweigh the benefits.

Question 2. Do ephedrine alkaloids pose the same risk for hemorrhagic stroke as phenylpropanolamine (PPA)?

Ephedrine alkaloids are sympathomimetic amines that affect the cardiovascular system by increasing blood pressure and heart rate. Ephedrine also is a central nervous system (CNS) stimulant. Based on the voluntary AERs reported to the FDA, the most serious adverse events associated with ephedrine alkaloids have been those that would be expected of potent sympathomimetic amines, including cardiac arrhythmias, myocardial infarctions, sudden death, strokes, and seizures.

Phenylpropanolamine (PPA) is a *synthetic* sympathomimetic amine that was used in numerous over-the-counter (OTC) medications as a decongestant and for weight loss. Recently, PPA was withdrawn from the United States market by the FDA after a study showed that this compound resulted in an increased risk, albeit small, of hemorrhagic stroke.

Absent a well-controlled clinical study comparing ephedrine alkaloids to PPA, it is not possible to answer the question of whether ephedrine alkaloids pose the same increased

risk for hemorrhagic stroke as PPA. While the AMA supports well-controlled clinical studies on the relationship of serious adverse events to ephedrine alkaloids, these studies are not a necessary prerequisite to removing dietary supplement products containing ephedrine alkaloids from the market immediately.

Question 3. Should herbal ephedra be available by prescription only in the United States?

For reasons stated above, the AMA strongly supports the removal of dietary supplement products containing ephedrine alkaloids from the United States market. Whether products containing ephedrine alkaloids that are regulated as drugs should be available in the United States remains an open question. A product ~~sponsor (manufacturer) would~~ have to submit evidence of safety and efficacy for one or more indications to the FDA for premarket review. If the evidence shows a benefit/risk ratio that justifies approval for marketing, then such a product could be marketed. Whether the product is available OTC or only by prescription would depend on the product's safety and on the need or lack of need for physician supervision of patients using the product.

Question 4. What are the dangers of taking ephedra-containing products without medical supervision?

Because of ephedrine's known sympathomimetic effects on the cardiovascular and central nervous systems, reports of cardiac arrhythmias, myocardial infarctions, sudden death, strokes, and seizures are not unexpected. These types of severe adverse events have been reported in the medical literature for many years. If individuals have a known pre-existing condition (e.g., cardiovascular disease) that makes them more susceptible to these complications of ephedrine, then medical supervision could prevent the complication from occurring (e.g., by advising the patient not to use ephedrine). Ephedrine rarely is used today for medical purposes because many other drugs are more effective and have fewer adverse reactions. However, if a physician were to recommend ephedrine for medical purposes, the risks could be weighed against the benefits.

As discussed above, the real problem with dietary supplements containing ephedrine alkaloids is that there is no, or at best questionable, benefit in using the product. No medical condition or illness is prevented by having ephedrine in your diet. Yet ephedrine alkaloid-containing products do have risks and, in some cases, these risks may be serious or fatal to previously healthy young people who do not experience any benefit from the product. These serious side effects, regardless how rare they may be, are unacceptable in the absence of proven benefits, and the products should be removed from the market.

Question 5. Please explain the difference between a patient taking a prescription drug for obesity under the supervision of a physician and a consumer taking an ephedra product for obesity without any screening for medical conditions that would suggest that the consumer was a poor candidate for such a product.

Appropriate treatment of overweight and obese patients requires a comprehensive approach involving diet and nutrition, regular physical activity, and behavioral change, with an emphasis on long-term weight management rather than short-term extreme weight

reduction. The aggressiveness of the treatment approach should be tailored to match the health risks associated with the patient's weight. Available treatment options vary in their effectiveness and risk. Physicians have an important role in promoting preventive measures and encouraging positive lifestyle behaviors, as well as identifying and treating obesity-related comorbidities. Physicians also fulfill a vital function in counseling patients about safe and effective weight loss and weight-maintenance programs, referring patients to ancillary personnel when appropriate, and providing monitoring, support and encouragement to the patient.

Prescription anti-obesity drugs should be given only as an adjunct to nutrition therapy and exercise. The AMA concurs with the following ~~NIH recommendations~~ for the pharmacologic treatment of adult obesity:

- lifestyle therapy (diet, exercise) should be considered before any drug therapy;
- weight-loss drugs approved by the FDA may be used as part of a comprehensive weight-loss program for patients with a body mass index (BMI) $\geq$ 30 kg/m^2 with no accompanying obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary heart disease, type 2 diabetes, and sleep apnea), and for patients with a BMI $\geq$ 27 mg/m^2 with accompanying obesity-related risk factors or diseases;
- avoid use of drugs without accompanying lifestyle modification;
- assess drug efficacy and safety continually;
- discontinue drug use if it is ineffective in weight loss or weight maintenance, or if there are serious side effects. Pharmacotherapy cannot be expected to continue to be effective in weight loss or weight management after cessation of drug therapy.

To prevent weight regain, weight-loss drugs need to be used on a long-term basis in the same fashion as agents for other chronic disorders, such as hypertension, hyperlipidemia, and diabetes. In order to be used on a long-term basis, weight-loss medications must be both safe and effective. Because many obese patients have underlying cardiovascular and endocrine conditions, physicians should be involved to monitor for adverse effects, as well as drug efficacy.

Dietary supplements (e.g., ephedra alkaloids in combination with caffeine) that promise quick and easy weight loss without physician supervision are attractive to consumers. However, combining the stimulants caffeine and ephedra, particularly without medical supervision, may increase the risk of adverse events. Additionally, poor quality control may contribute to the problems associated with the safety and efficacy of ephedra-containing dietary supplements. No two ephedra-containing supplements are the same. They contain multiple alkaloids of varying potency, and significant differences between label claims and actual contents of ephedra alkaloids have been noted, both among within specific products. The AMA continues to be concerned that the FDA has not, as of this date, released proposed regulations for Good Manufacturing Practices for dietary supplements.

As noted earlier, because of the unpredictable amounts of active ingredients and the potential for harmful side effects, the NIH guidelines for the treatment of obesity state that herbal preparations, including ephedra-containing products, are not recommended as part

of a weight-loss program. Without medical supervision, some individuals who might be discouraged by previous failures to lose weight may combine medications, or use dietary supplements at doses higher than what is recommended.

Question 6. Please discuss any initiatives that the AMA has taken to ensure that in discussing weight loss with their patients, physicians explain the possible dangers of ephedra-containing products.

The AMA is currently developing a document entitled "Assessment and Management of Adult Obesity: A Primer for Physicians and Other Health Professionals." One component of this guide deals with pharmacologic management and will address the role of dietary supplements for weight loss. This document is expected to be released next year. When it is issued, the AMA would be pleased to share this primer with members of the Subcommittee.

Thank you for the opportunity to testify before the Subcommittee. The AMA looks forward to working with you to protect patients' health.

Testimony of Sidney M. Wolfe, MD
Director, Public Citizen Health Research Group, Washington DC
Before Senate Governmental Affairs Committee, Subcommittee on Oversight of Government Management
Hearing on Dangers of Ephedra
October 8, 2002

Senator Durbin and members of the Subcommittee, thank you for the opportunity to testify on this important topic. Your hearing is essential because of the extreme, reckless negligence exhibited by dietary supplement companies who continue to sell ephedra-containing products and because of the industry-enfeebled Department of Health and Human Services, including the FDA, that has thus far allowed the companies to get away with continuing to manufacture and push these deadly drugs.

The US Military Puts the HHS and the FDA to Shame

From 1997 through part of 2001, there have been 30 deaths among active duty personnel in the armed forces (Army, Air Force, Navy and Marines) in people who were using ephedra alkaloids. All were between the ages of their early 20's and early 40's and had been in good health prior to their deaths. There was no other explanation for their deaths. Since then, there have been three additional deaths associated with the use of ephedra products in the Army alone.[1]

Partly as a result of these 33 deaths and other serious, non-fatal adverse events in the military associated with ephedrine, in July of this year memos were sent to all Army and Air Force military exchanges and commissaries worldwide stating that by the end of August (2002), all ephedra-containing products should be removed from the shelves in these military posts for six months until the results of the HHS ephedra review are released. According to a recent Army/Air Force bulletin, from Fort Monroe, Va. (August 19, 2002)--"Training and Doctrine Command has joined with Forces Command in asking the Army Air Force Exchange Service to remove products containing ephedra, a compound normally found in diet products." It is extremely important that in explaining the basis for issuing this order, Dr. DeKonning, an army physician, stated that "The sale of ephedra-containing products by facilities on TRADOC [training and doctrine command] installations is seen by our soldiers as an affirmation that their use is safe and acceptable."[2]

The U.S. Marine Corps had earlier--in February 2001--banned the sale of ephedra-containing products on its military bases: "The Commandant of the Marine Corps banned the sale of dietary supplements containing ephedra alkaloids, or ephedrine, at Marine Corps Exchange stores worldwide as of February 1.[3]

Sixteen months ago, the Canadian government warned Canadians "not to use products containing the herb Ephedra" because such products "may cause serious, possibly fatal, adverse effects." On January 9 of this year, Health Canada requested a recall of all ephedra products "with labeled or implied claims for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects."

In answering the questions you have provided me, I will add, to the published references in our petition, information obtained since it was filed.

What is the basis for our September, 5, 2001 HHS petition (filed with Dr. Ray Woosley, now of the University of Arizona) to ban the manufacture and sale of all ephedra-containing dietary supplements?

The answer to this question must start out with two other questions:

Do drugs which are related to epinephrine (adrenaline) such as ephedrine, phenylpropanolamine, amphetamines and similar drugs cause an increase in blood pressure, constriction of blood vessels, an increase in heart rate or an increase in cardiac arrhythmias? The answer is unequivocally yes, and this has been known for decades.

Is there evidence that these drugs can cause strokes and heart attacks in people because of causing an increase in blood pressure, constriction of blood vessels, heart rate or cardiac arrhythmias?

In addition to the section in our petition presenting evidence for cardiovascular toxicity of ephedra (see appendix), we have obtained a copy of an internal March 28, 2000 FDA memo from Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) in response to being asked to review the strength of the evidence linking ephedra with life-threatening cardiovascular events and strokes. After a review by CDER's Office of Postmarketing Drug Risk Assessment (OPDRA), Dr. Woodcock concluded that "...at least 108 of the reports [clinically significant cardiovascular and central nervous system adverse event reports] OPDRA analyzed provide very strong evidence in support of a causal relationship between EADS [ephedra alkaloid-containing dietary supplements] and the adverse events, particularly in light of the known pharmacodynamic effects of ephedrine alkaloids."[4]

What is the incongruity in FDA banning PPA (phenylpropanolamine) but allowing ephedra to stay on the market?

Given that there are now more reported cases of death, heart attacks, stroke and other adverse effects associated with ephedra than with PPA at the

time of its ban, the situation represents a dangerous déjà vu. We are now, with ephedra, where we were 10 years ago with PPA: clear, unequivocal evidence of danger but a time-delaying "need" by the industry to conduct studies. (FDA unfortunately bought into the need for a case control study on PPA 10 years ago). With PPA, dozens or more lives were lost and many people permanently disabled between the time the FDA clearly should have acted and when they finally got the drug (PPA) off the market. To repeat this fatal mistake with ephedra is to fail to learn the lessons of history.

Since we have petitioned the FDA to ban other weight loss products such as Meridia (sibutramine, Abbott), what benefit/risk analysis should be applied to weight loss products?

Over 30 years ago, in June 1968, FDA Medical Officer Dr. Robert O. Knox refused to approve the New Drug Application (NDA) for a diet drug. This disapproval touched off a dispute between the FDA and the drug's manufacturer, A.H. Robbins, that eventually led to the drug's approval and Dr. Knox's transfer to another area within the Agency. His reason: obesity is a chronic disease and there is no evidence that these drugs affect the course of the disease over the long term.

The drug Dr. Knox refused to approve was fenfluramine (Pondimin), a drug that ultimately became the "fen" portion of the notorious "fen/phen" combination, the portion that was removed from the market on September 15, 1997 because it caused heart valve damage and a potentially fatal adverse reaction of the lungs known as primary pulmonary hypertension.

At the time of our petition to ban Meridia on March 19th of this year, there were 19 reported cardiovascular deaths in people using the drug, again, far fewer than the number with ephedra. The fact that there is no evidence of long-term benefit with either drug and there is evidence of shorter-term risk means that the benefit/risk ratio for both is extremely unfavorable to patients.

Discuss what is known about the dosages taken by those experiencing serious adverse effects from ephedrine/ephedra. Is there a safe dose?

In a recent published review of FDA adverse reaction reports by researchers from New England Medical Center in Boston, in 36 of 37 patients with heart attacks, strokes or sudden deaths, the use of ephedra (ma huang) was reported to be within the manufacturers' dosing guidelines.[5] There are also a number of reports in which a so-called pharmacologic autopsy--post-mortem measurement of urine, blood and tissue levels--found low levels of ephedra consistent with recommended use. Given that there is no standardization of the amount appearing in the product and, more importantly, that there is enormous variation from person to person in sensitivity to such drugs, no dose is the only safe dose.

Discuss the effects that additional compounds such as caffeine have on the safety profile of ephedra, given that it is usually sold in combination with such stimulants.

Both caffeine and ephedra can stimulate the sympathetic nervous system so their combined use increases the cardiovascular risks. In addition, the frequent use of these products in the context of exercise, also a stimulant to the sympathetic nervous system, makes for a triple dose of stimulation--in combination with ephedra and caffeine--which probably accounts for the growing number of deaths while young, otherwise healthy people are exercising.

In July 1995, according to the agency, "FDA proposed banning OTC bronchodilators containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride because of abuse and misuse. According to the U.S. Drug Enforcement Administration, ephedrine is being used to make illegal drugs. And, the FDA has found that some drug manufacturers promote ephedrine for unapproved uses, such as weight control and muscle enhancing." The fact that the FDA has not finalized this proposed ban of ephedrine in OTC products should not be used as an excuse for the failure to ban dietary supplements containing ephedra. The proposed OTC ban is still in the works.

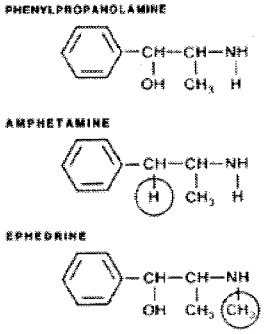
This is not and has never been a question of scientific or medical evidence. It is a question of politics, and the extraordinarily dangerous political cowardice of the FDA and HHS Secretary Thompson in the face of massive lobbying by ephedra-makers in Washington. Is the FDA still part of the Public Health Service or is it a drug sales promoting adjunct to the pharmaceutical and dietary supplements industries? De facto drug pushers include those who refuse to use their legal authority to remove a well-documented hazard to the public health from the market. There is no doubt that these products will be banned in the United States. The question is not whether, but when. Delaying tactics such as the Rand review are costing lives as the day of reckoning for ephedra is thereby delayed. There are few issues that the AMA and Public Citizen agree on. Tobacco and ephedra are two of these. The FDA has been rejecting the opinions of its own consultants and staff (such as Dr. Woodcock) on the dangers of ephedra alkaloids.

Appendix

The FDA funded the review by Benowitz, which found hypertension to be the most common manifestation of ephedrine alkaloid dietary supplement toxicity.[6] Zahn reports a 21-year-old man presenting to the emergency department with a blood pressure of 220/110 after ingesting *herbal ecstasy*, a common name for an ephedrine alkaloid dietary supplement.[7]

Sixty-nine cases of ephedrine alkaloid dietary supplement associated stroke are represented in the SN/AEMS data set. Ephedrine alkaloid dietary supplements account for 81% of all dietary supplement related strokes. Alarmingly, stroke has been reported with the use of an ephedrine alkaloid dietary supplement in an individual of exceptional health without any other known risk factors for a cerebrovascular accident.[8] Bruno et al. report three separate incidences of stroke associated with the use of street drugs containing ephedrine exclusively[9] and the Hemorrhagic Stroke Project documented the increased susceptibility to stroke found in women using phenylpropalamine (PPA), a metabolic breakdown product of ephedrine and another member of the ephedrine alkaloid family.[10] A vasculitis-like beading pattern of the cerebral arteries is a common factor to many of the ephedrine alkaloid stroke reports. [11,12,13]

The following chart shows the close chemical structures of PPA, ephedrine and amphetamine. Notice that PPA is identical to ephedrine except for the absence of a methyl (CH3) group. In fact, the body metabolizes a small portion of ephedrine to PPA which is also called norephedrine (nor meaning no methyl group).



Ephedrine dietary supplements have been implicated in 62 instances of arrhythmia in the SN/AEMS data set. Zahn reports ventricular arrhythmia temporally associated with a patient's use of an ephedrine alkaloid dietary supplement.[14] The patient stabilized after emergent treatment with lidocaine. Such ventricular arrhythmia may easily degenerate into ventricular fibrillation and cardiac arrest as described by Haller and Benowitz.[15] In the over the counter medication market, ephedrine alkaloid based cold medications have been shown to induce arrythmias. Pseudoephedrine, at recommended doses, was implicated in causing an arrhythmia in a healthy man with no known risk factors.[16] Onuigbo's case report of arrhythmia in a pregnant woman shows that unwittingly combining sympathomimetics places patients at perilous risk.[17] The fact that all of the cases of arrhythmia resolve and fail to recur in the absence of the offending agent is compelling evidence in favor of ephedrine alkaloid's causal role.

Coronary vasospasm due to the ingestion of sympathomimetics has been shown to result in chest pain and myocardial infarction / heart attack. Ephedrine alkaloid dietary supplements contributed to 88 reports of chest pain and 32 cases of myocardial infarct / heart attack in the SN/AEMS data set. Traub reports a 19-year-old male bodybuilder who suffered an inferolateral myocardial infarction after using the recommended dosage of an ephedrine alkaloid dietary supplement.[18] This patient had no known risk factors for heart disease and no significant findings on cardiac catheterization. In a controlled cross-sectional study of chest pain admissions at a pediatrics emergency department, James found that ephedrine exposure was associated with chest pain in adolescents.[19] Wiener describes a 28-year-old man with no known cardiac risk factors who suffered a myocardial infarct after taking the recommended dose of a pseudoephedrine decongestant.[20] This apparently inherent ability of ephedrine alkaloids to provoke chest pain and induce myocardial infarction in healthy patients is of particular concern because of the implications for vulnerable patients using other medications or with previously undiagnosed underlying medical conditions. Note that some of these adverse cardiovascular events can occur at the recommended dose.

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[1] Telephone conversation with Mike Heath, Pharm.D. Senior Pharmacist, U.S. Army, Consultant for the US Army Surgeon General, Washington DC.

[2] Announcement of recent Army/Air Force worldwide ban of sale of ephedra-containing products in military exchanges. A similar memo was sent concerning the ban of sales in commissaries (these are different from exchanges. http://www.army.mil/usar/news/2002/08august/ephedra.html (Accessed October 7, 2002)

[3] Announcement from Marine Corps Air Station Miramar, February 9, 2001. Order issued by General James L. Jones.

[4] Memo from Dr. Janet Woodcock, March 28, 2000, to FDA CFSAN (Center for Food Safety and Nutrition) Director Joe Levitt.

[5] Samenuk D, et al. Adverse cardiovascular events temporally associated with Ma Huang, an herbal source of ephedra. Mayo Clin Proc, 2002;77:12-16.

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[15] Haller, op. cit.

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STATEMENT OF FRANK D. URYASZ, PRESIDENT,
THE NATIONAL CENTER FOR DRUG FREE SPORT, INC.
AND A REPRESENTATIVE FOR
THE NATIONAL COLLEGIATE ATHLETIC ASSOCIATION
BEFORE THE GOVERNMENTAL AFFAIRS SUBCOMMITTEE ON
OVERSIGHT OF GOVERNMENT MANAGEMENT, RESTRUCTURING AND THE
DISTRICT OF COLUMBIA
UNITED STATES SENATE
OCTOBER 8, 2002
EPHEDRA: WHO IS PROTECTING AMERICAN CONSUMERS?

Chairman Durbin and other distinguished members of the Subcommittee, on behalf of the National Collegiate Athletic Association, thank you for inviting the NCAA to appear today to inform you of the Association's activities as they pertain to the substance "ephedra."

I am Frank D. Uryasz, president of The National Center for Drug Free Sport, Inc. The Center is a for-profit corporation based in Kansas City, Missouri. Our company provides drug-education and drug-testing services to sports organizations, colleges, universities and high schools. Our clients include the NCAA, NFL and many colleges and universities.

Prior to starting The Center, I was director of sports sciences for The National Collegiate Athletic Association from 1986 through 1999. As director of sports sciences, I was responsible for managing the NCAA health and safety programs, which included the national drug-testing programs.

Currently, Drug Free Sport administers the NCAA's national drug-testing programs. For this reason, the NCAA asked me to represent it here today. Also present with me today are Mary Wilfert and Abe Frank from the NCAA national and Washington offices.

The NCAA is a private association of approximately 1,200 four-year colleges, universities and athletics conferences. Approximately 360,000 student-athletes compete in intercollegiate athletics at these institutions.

One of the guiding principles of the NCAA is in the area of athlete health and welfare. The NCAA manual states that it is the responsibility of each member institution to protect the health and safety and provide a safe environment for each of its participating student-athletes.

The NCAA schools take this responsibility seriously and the NCAA commits significant resources to its schools to ensure that athletes' health and safety are maximized. These resources include:

- The NCAA Committee on Competitive Safeguards and Medical Aspects of Sports. This committee is a full standing committee of the Association. Its sole purpose is to advise the NCAA and its members on matters regarding health and safety.

- The NCAA Sports Medicine Handbook. A set of sports medicine guidelines for member schools that includes the NCAA's recommendations on educating athletes about dietary supplements.
- Health and safety specialists. The NCAA national office employs staff members who oversee the NCAA's health and safety initiatives.
- Two national drug-testing programs designed to deter the use of NCAA banned drugs.
- Educational seminars on developing student-athlete drug and supplement prevention programs within the university.
- National survey research on the drug and supplement use and abuse habits of college athletes.

These are a just a few of the many ways that the NCAA commits its resources to helping student-athletes maintain or enhance their health.

Since 1985, the NCAA has conducted a national study of the drug and supplement use habits of college athletes. The study is replicated every four years and four replications have been conducted since the original study. The study is designed to obtain data on the substances and use patterns of college athletes through the use of anonymous self-report questionnaires. Over 21,000 student-athletes completed the survey in the 2001 study. Copies of the study are available at www.ncaa.org and are available at the hearing today.

Prior to the 1997 replication, the NCAA competitive safeguards committee had been monitoring reports of the growing use of dietary supplements, including ephedrine, by college athletes. Accordingly, the committee included questions about the use of supplements on the 1997 survey. The 1997 study found the following regarding college athletes' use of ephedrine:

- 3.5% of the athletes surveyed reported using ephedrine within the previous 12 months.
- The highest rate of ephedrine use among male athletes was in wrestling (10.4%); the highest for women was in soccer (3.3%).
- 50.8% of users said they used ephedrine primarily to improve athletic performance.
- Athletes used ephedrine more in the competitive season, started their use in high school and many used right before or during practice or competition.

Although the study showed that a small percentage of athletes was using ephedrine, the NCAA was concerned that its use was being linked so closely with the desire to improve athletic performance. For this reason, the competitive safeguards committee recommended in July 1997 that ephedrine be included on the list of banned drugs by the NCAA. The NCAA membership agreed with this recommendation and ephedrine remains on the list to this day.

The NCAA sponsors two national drug-testing programs for college athletes. As part of its drug-prevention efforts, the NCAA publishes a list of banned drug classes and tests athletes periodically. The NCAA list, like most banned-drug lists of national and international sports organizations, includes stimulants. Ephedrine is included on that list.

The NCAA drug-testing programs are designed to deter the use of banned drugs. The NCAA believes testing is necessary to protect the athletes' health and safety and to ensure that athletes are not using performance-enhancing drugs to gain a competitive advantage.

The NCAA instituted drug testing at its championships and post-season football bowl games in 1986. Since 1986, any NCAA athlete competing in these events is subject to NCAA drug testing under a strict, published protocol utilizing the best laboratory in the U.S. for sports drug testing. Approximately 1,500 athletes are tested each year. Athletes who test positive lose their eligibility to compete in all sports for at least one year. Since the 1997 ban on ephedrine, all athletes who participate in NCAA drug testing have been tested for ephedrine use.

To deter the use of training drugs such as anabolic steroids, the NCAA implemented a second drug-testing program in August 1990. Today as part of this program, over 10,000 athletes are tested by the NCAA on their campuses August through June. Stimulant testing was not included in this testing program.

The 2001 replication of the NCAA's national drug use survey provided new data on how athletes' use of ephedrine changed from the 1997 survey.

- Ephedrine use had grown from 3.5% in 1997 to 3.9% in 2001.
- The highest use in men's sports was now in lacrosse (5.5%) and in women's gymnastics (8.3%).
- Most started using ephedrine in high school.
- Users stated that they used ephedrine to improve performance (24%), as an appetite suppressant (22%), for health reasons (22%) and to improve appearance (20%).

Due in large part to the 2001 survey findings, the NCAA added ephedrine testing to its year-round drug-testing program in August 2002. This year, NCAA will conduct over 10,000 drug tests for ephedrine.

It should be noted that the NCAA ban on ephedra is part of an overall ban on the use of stimulants. Athletes will use stimulants to increase their energy levels and to help them lose weight or body fat. The use of stimulants combined with exercise and heat can cause damaging health effects and even sudden death.

The NCAA's prevention efforts as they pertain to ephedra(ine) are significant. They include:

- The Dietary Supplement Resource Exchange Center (REC). All NCAA athletes may use this service funded by the NCAA and housed at Drug Free Sport. The REC provides a toll-free number and Web site for athletes to get reliable information about the effects of supplement use. Inquiries are treated in a confidential manner. The REC has an ongoing relationship whereby any reports of health effects of supplement use are reported to the FDA's Medwatch program.
- Educational information via bookmarks and on the Web at www.drugfreesport.com.

- Posters explaining the consequences of supplement use.
- Educational conferences for coaches and administrators on deterring supplement use by athletes.
- A national speakers bureau of experts on drug and supplement use in sport.
- The NCAA also communicates through its biweekly publication, The NCAA News, which has featured a number of articles on supplement use. A special advisory memorandum from the NCAA also was sent June 5, 2001, copies of which are available today at the hearing.

All NCAA colleges have agreed through formal legislation not to distribute supplements to athletes unless the products fall into specific, restricted categories such as fluid replacement drinks or vitamins and minerals. Ephedra is not provided under any circumstances.

Ephedra(ine) can be found in a multitude of sports supplements that are marketed to NCAA athletes. Everything from "energy bars," to "power drinks" to supplement pills and capsules, all of which are legally obtainable, contain ephedra, ephedrine or ma huang. Product manufacturers target young, active people with ads that tout the performance enhancing benefits of cutting fat and increasing energy. Such ads refer to ephedrine as a "natural way" to achieve superior performance. It is fair to say that those of us who educate young people on the dangers of supplement use feel like the proverbial lone voice in the wilderness of supplement marketing.

The NCAA remains committed to reducing the demand-side of the dietary supplement problem in sport. Its testing, education and prevention programs are based on national research, administered at the highest level and with the greatest oversight possible. The NCAA wishes to make known today that it is a willing partner in any national effort that will enhance the health and safety of its athletes.

Thank you.

Frank D. Uryasz
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On behalf of
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

LESTER M. CRAWFORD, D.V.M, Ph.D.

DEPUTY COMISSIONER

FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT OF GOVERNMENT
MANAGEMENT, RESTRUCTURING, AND THE
DISTRICT OF COLUMBIA

COMMITTEE ON GOVERNMENTAL AFFAIRS

UNITED STATES SENATE

OCTOBER 8, 2002

RELEASE ONLY UPON DELIVERY

THE REGULATORY FRAMEWORK UNDER THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT (DSHEA) OF 1994

In 1994, DSHEA created a unique regulatory framework for dietary supplements in the United States. Its purpose was to strike the right balance between providing consumers access to dietary supplements that they use to help maintain and improve their health and giving the Food and Drug Administration (FDA or the Agency) the necessary regulatory authority to take action against supplements that present safety problems, have false or misleading claims, or are otherwise adulterated or misbranded.

I reference the July 31, 2002 testimony before your subcommittee of Joe A. Levitt, Director of FDA's Center for Food Safety and Applied Nutrition (CFSAN). In that testimony we detailed FDA's actions as we commenced our regulatory and enforcement actions under DSHEA.

As a summary of the previous testimony, I would like to point out that the DSHEA regulatory framework for dietary supplements is primarily a postmarket program, as is the case for foods in general. Should safety problems arise after marketing, the adulteration provisions of the statute come into play.

Under DSHEA, a dietary supplement is adulterated if, among other things, it or any of its ingredients presents "a significant or unreasonable risk of illness or injury" when used as directed on the label, or under normal conditions of use if there are no directions. FDA

bears the burden of proof to show that a product or ingredient presents such a risk. In addition, the Secretary of Health and Human Services (HHS) has the authority to declare that a dietary supplement or dietary ingredient poses an "imminent hazard" to public health or safety.

FDA recognizes the success of our effort will depend on new and continued partnerships with other government agencies, academia, health professionals, industry and consumers. The Agency is committed to continue its outreach to stakeholders by establishing stronger working relationships with them as well as leveraging resources and communicating accurate dietary supplement information. As part of its implementation guidance, in May 2002, FDA provided Congress with a "Dietary Supplement Strategic Plan Cost Out."

THE DIETARY SUPPLEMENT – EPHEDRA

The focus of this hearing is on ephedra. Congress defined the term "dietary supplement" in DSHEA. A dietary supplement is a product that, among other requirements, is ingested, is intended to supplement the diet, is labeled as a dietary supplement, is not represented as a conventional food or as a sole item of a meal or the diet, and contains a "dietary ingredient." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and dietary substances such as enzymes. Dietary ingredients also can be metabolites, constituents, extracts, concentrates, or combinations of the preceding types of ingredients. Dietary supplements may be found

in many forms, such as tablets, capsules, liquids, or bars. DSHEA placed dietary supplements in a special category under the general umbrella of "foods," except where the product meets the drug definition.

Ma huang is one of several names for herbal products containing members of the genus Ephedra. A number of adverse effects, including hypertension (elevated blood pressure), palpitations (rapid heart rate), neuropathy (nerve damage), myopathy (muscle injury), psychosis, and memory loss, or even the more serious adverse effects of heart attacks, stroke, seizure and death, have been reported to FDA with products containing Ma huang or other species of Ephedra as ingredients. Adverse events related to these products are currently under investigation. Ephedra has been shown to contain various chemical stimulants, including the alkaloids ephedrine, pseudoephedrine and norpseudoephedrine, as well as various tannins and related chemicals.

The concentrations of these alkaloids depend upon many factors, such as the species, parts of the plant used, time of harvest, and geographical location. Ephedrine and pseudoephedrine are used in over-the-counter and prescription drugs. Many of these stimulants have known potentially serious side effects. Ephedra is sold in products for weight control, as well as in products promoted to boost energy levels or to enhance athletic performance. These products often contain other stimulants, such as caffeine, that may have synergistic effects and increase the potential for adverse effects.

FDA Advisory Committees – 1995-1996

In 1995, FDA convened a Working Group of the Food Advisory Committee Meeting on ephedra. They reviewed all the safety information available, including the known published literature on pharmacological issues and adverse event reports submitted to the Agency. This was followed in August 1996 by a meeting of FDA's Food Advisory Committee. The prevailing view coming out of these meetings was that FDA should seek to establish a safe dose for ephedra products.

FDA Proposed Rule – June 4, 1997

On June 4, 1997, FDA published a proposed rule on dietary supplements containing ephedrine alkaloids. Under the proposed rule, a dietary supplement would be adulterated if it contained eight milligrams (mg) or more of ephedrine alkaloids per serving, or if its labeling suggested or recommended conditions of use that would result in an intake of eight mg or more within a six-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids. The Agency also proposed to prohibit the use of ephedrine alkaloids in dietary supplements with other stimulants, such as caffeine; to require special labeling on dietary supplements containing ephedrine alkaloids, including a warning statement and a statement that the product should not be used for more than seven days; and to prohibit labeling claims that require long-term intake to achieve the purported effect (e.g., claims about weight loss or body building). FDA received over 14,000 comments, the vast majority opposing the proposed rule.

General Accounting Office (GAO) Study – May 1998

In May 1998, the House Committee on Science requested that the GAO examine the scientific basis for the ephedrine alkaloids proposal. On August 4, 1999, GAO released its report entitled: "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids."

While GAO concluded that FDA was justified in determining that the number and nature of adverse event reports relating to dietary supplements containing ephedrine alkaloids warranted the Agency's attention, they expressed concerns about the use of the reported adverse events to support the proposed dosing level and the limit on duration of use. The GAO concluded that the Agency needed additional evidence to support these restrictions, recommending FDA "provide stronger evidence on the relationship between the intake of dietary supplements containing ephedrine alkaloids and the occurrence of adverse reactions that support the proposed dosing level and duration of use limits."

Partial Withdrawal of Proposed Rule & Review of Adverse Events – April 3, 2000

On April 3, 2000, FDA withdrew the portions of the ephedrine alkaloids proposed rule relating to the dosing level and duration of use limits for these products. It retained the proposed warning statement and prohibition on including other stimulant ingredients in

dietary supplements containing ephedrine alkaloids. At the time of the partial withdrawal of the proposed warning statement, FDA stated that the Agency continues to have a public health concern about the use of dietary supplements containing ephedrine alkaloids. FDA announced the public release of additional adverse event reports (AERs) that FDA had collected since 1997, which brought the number of adverse events up to approximately 1,400 reports at that time. The Agency also released the results of separate reviews by two scientific divisions within FDA and four outside scientific experts, of all AERs on ephedra received by FDA between June 1, 1997 and March 31, 1999, approximately 160 AERs. These separate reviews concluded that a significant number of these AERs were probably or possibly associated with ephedra use. FDA also sought public input about the significance of the new information and expert reviews and requested the submission of any other information relevant to a safety assessment of these products.

HHS Public Meeting – August 2000

The Department of HHS Office of Women's Health (OWH) held a public meeting on ephedra in August 2000. FDA and two of its outside experts presented their reviews of the 160 AERs referenced above. Industry representatives and their scientific experts also made presentations, as did some consumers and others. In September 2000, OWH issued its report on ephedrine alkaloid dietary supplements (EADS) from the public meeting. They concluded:

"Despite the established limitations of AERs, many of the adverse effects are biologically plausible based on the known pharmacologic effects of ephedrine alkaloids. The pharmacology of ephedrine is supported by a rich database, in contrast to the paucity of evidence on the benefits or risks of EADS in humans. The level of concern for continued use of EADS must be based on the totality of information available on ephedra and ephedrine alkaloids, including the AERs, results of human and animal studies, as well as what is known about the pharmacology and chemistry of these compounds.

Given the current widespread use of EADS, a consumer education campaign about these products is warranted. Good manufacturing standards are needed, reasonable dose and duration levels determined, and warnings and contraindications clearly indicated on labels. A research agenda should be established. Therefore, the research community should take the next logical step by conducting a systematic review of the world's literature on ephedra. After compiling the state of the science and identifying the limitations and gaps of the current research, an appropriate agenda can be established. In this regard, the National Center for Complementary and Alternative Medicine of the National Institutes of Health already is requesting proposals to study herb-drug interactions."

New England Journal of Medicine – November 2000

In November 2000, the New England Journal of Medicine published an advance Internet copy of a review of 140 ephedra AERs by Drs. Christine Haller and Neil Benowitz. The results of the study showed that 31% of the cases were considered to be definitely or probably related to the use of supplements containing ephedra alkaloids and 31% were deemed to be possibly related. Among the adverse events that were deemed definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids, 47% involved cardiovascular symptoms and 18% involved the central nervous system. Hypertension was the single most frequent adverse effect (17 reports), followed by palpitations, tachycardia or both (13); stroke (10); and seizures (7). Ten events resulted in death and 13 events produced permanent disability, representing 26% of the definite, probably and possible cases. The article concluded: "the use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons. These findings indicate the need for a better understanding of individual susceptibility to the adverse effects of such dietary supplements." I do want to call the subcommittee's attention to the fact that the article was based upon an expert review of some adverse events that FDA had provided Dr. Benowitz, as an FDA consultant.

Department of HHS's Office of Inspector General (OIG) – February 12, 2001

On February 12, 2001, the OIG published a report: "Adverse Event Reporting for Dietary Supplements: An Inadequate Safety Valve." They made four recommendations:

1. Facilitate greater detection of adverse events by requiring manufacturers to report to FDA and to conduct greater outreach to health professionals and consumers;
2. Obtain more information on adverse event reports to generate stronger signals by establishing manufacturer and product registries and developing a new computer data base;
3. Obtain more information to assess signals by exploring the possibility of a monograph system, expedite the development of good manufacturing practices and assist the industry in standardizing ingredients; and
4. Disclose more useful information to the public.

The recommendation to require adverse event reporting for dietary supplements requires a change in the current law. Meanwhile, FDA has made changes in other areas, as a result of the OIG report. The dietary supplement adverse events reporting system is being greatly improved with the implementation of the new CAERS system next year. On September 17, 2002, FDA did a public outreach on a new action we will take when we are notified about an adverse event. Our new procedure will be to send a letter to the supplement manufacturer or distributor to alert them to the event. Also, the recently enacted Bioterriorism law requires both conventional food and dietary supplement

manufacturers to register with FDA. FDA is currently drafting proposed regulations to implement this requirement.

Public Citizen Petition – September 5, 2001

On September 5, 2001, Public Citizen and Dr. Ray Woolsey petitioned HHS to ban the production and sale of dietary supplements containing ephedrine alkaloids on the basis that these products present "a significant or unreasonable risk of illness or injury." They claimed that these products are being promoted to young people as athletic performance enhancers. Public Citizen cited a March 2001 Health Canada advisory warning consumers not to use products containing ephedra. On January 31, 2002, Public Citizen petitioned HHS once again to ban products containing ephedra.

Mayo Clinic Proceedings – January 2002

The January 2002 *Mayo Clinic Proceedings* published an article "Adverse Cardiovascular Events Temporally Associated With Ma Huang, an Herbal Source of Ephedrine." They analyzed 37 patients and found: (1) ma huang use is temporally related to stroke, myocardial infarction, and sudden death, (2) underlying heart or vascular disease is not a prerequisite for ma huang-related adverse events, and (3) the cardiovascular toxic effects associated with ma huang were not limited to massive doses.

They concluded that observational and circumstantial evidence indicates that use of the substance may be associated with serious medical complications.

Boozer Daly Study – February 2002

Drs. Boozer and Daly conducted a study on the utility, safety of a combination herbal preparation consisting of ephedrine alkaloids and caffeine in weight loss. This was accepted for publication in the International Journal of Obesity (IJO), February 2002, (volume 26, page 593-604). It was a six month placebo controlled trial with a total of 167 subjects. The authors concluded that the preparation promoted body weight reduction without significant adverse events in this study. The Department of HHS and FDA have discussed this study with Drs. Boozer and Daly on two occasions. We are seeking permission to receive raw data from this study, if needed, during our ongoing review. Also, there were two editorials that accompanied this article in IJO that cautioned about the selectivity of study participants.

RAND Study -- June 14, 2002

HHS recently funded the RAND Corporation to conduct a comprehensive review of the existing science on ephedrine alkaloids, particularly those in dietary supplements. The completion of the review is targeted for the early next year. The National Institutes of Health (NIH) will use this information, which will clarify the existing state of the science

on ephedrine alkaloids, to guide an expanded research effort to better understand the safety and efficacy of ephedrine alkaloids. RAND will be looking at adverse event reports, as well as published and unpublished clinical studies. This scientific review will help guide the Department and the Agency in developing future FDA regulatory actions on ephedrine alkaloids.

On a separate track, but at the same time, RAND has also been asked to conduct a dedicated review of a large number of documents from Metabolife. These include 13,000 consumer complaints and an additional 1,700 complaints with approximately 50 medical records. The completion for this review is targeted for later this year.

Metabolife Investigation – July 2002

In July 2002, FDA asked the Department of Justice (DOJ) to pursue a criminal investigation of Metabolife, to see if they had made false statements to FDA regarding the existence of adverse event reports. That investigation is ongoing at this time.

KEY FOR FDA – THE USE OF SOUND SCIENCE AND THE ABILITY TO OBTAIN NEEDED DATA

CFSAN Adverse Event Reporting System (CAERS)

Adverse events are the primary means FDA has for identifying potential safety problems with dietary supplements. Under DSHEA, FDA must rely on adverse event reports as a major component (i.e.—signal generator) of its post-market regulatory surveillance under DSHEA. Given that most experts estimate that adverse events actually reported to FDA range between 1% to 10% of actual occurrences, much time and resources have been devoted to making this system as effective as possible.

CAERS is a comprehensive computerized system that is being designed to capture and analyze all reports of consumer complaints and adverse events related to CFSAN-regulated products. This system will combine all existing Center adverse events reporting systems into one portal within CFSAN and create a state-of-the-art reporting and monitoring system that will serve as a post-marketing surveillance tool. Information gathered in CAERS will assist in the formulation and dissemination of CFSAN's post-marketing policies and procedures. Also, CAERS can provide a strong signal that is a guide toward further review of relevant scientific information.

In conjunction with the design and development of CAERS, CFSAN has developed and is currently staffing a new organizational unit within the Office of Scientific Analysis and

Support. This CAERS Staff will help coordinate and facilitate the processing of adverse event reports. The staff will also help to develop mechanisms to expedite and improve timely clinical assessment of dietary supplement adverse event reports. They will serve as the core functional unit for daily operations and will work in conjunction with contractors and Program Offices to ensure a consistent and efficient workflow.

PARTNERING WITH THE FEDERAL TRADE COMMISSION (FTC) -- 1997

"Operation Cure.All"

FDA also has enhanced its cooperation with FTC, through "Operation Cure.All" and other efforts. In 1997, FTC, FDA, Health Canada, and various State Attorneys General organized and implemented an ongoing and comprehensive law enforcement and consumer education campaign against the fraudulent marketing of supplements and other health products on the Internet. The agencies have moved to stop Internet scams for supplements and other products that purport to cure cancer, HIV/AIDS, and countless other life-threatening diseases.

FDA has made Internet surveillance an enforcement priority. The Agency's partnership with FTC, and others, in "Operation Cure.All" further demonstrates FDA's commitment to monitoring illegal conduct on the Internet. Collaboration on all "Operation Cure.All" activities maximizes FDA's effectiveness in communicating to the Internet community

that the various regulatory and law enforcement agencies are working together to combat health fraud. Activities are coordinated in order to ensure consistent results in areas where FTC, FDA, the States, and Health Canada have jurisdiction.

Since its inception, "Operation Cure.All" has resulted in hundreds of advisory letters directed at sites selling products with egregious claims as well as many enforcement actions directed against the marketing of fraudulent products.

The Agency has engaged in several consumer education efforts with FTC including a "Miracle Health Claims: Add a Dose of Skepticism" health fraud brochure. The brochure helps the consumer spot false and unsubstantiated claims and has suggestions on how to avoid being the target of health fraud.

Other Internet Activities – 1996-2002

As online activity has expanded over the past several years, FDA has sharpened its focus on the issue of Internet promotion, including products that are labeled as dietary supplements but are regulated as drugs because of their claims. In 1996, and again in 1999, FDA held public meetings to discuss and examine the issue of promoting, prescribing, and dispensing drugs online.

In January and February 2002, FDA and FTC participated in an International Internet search, led by the Australian Competition and Consumer Commission and with participation by 19 members of the International Marketing Supervision Network (IMSN), an organization made up of consumer protection agencies worldwide. As a result of the surf, FTC has sent over 280 advisory letters to domestic and foreign sites that were identified as making questionable claims for health-related products or services, dietary supplements. FDA is also making initial contact with Internet sites and alerting them to potential legal problems. The websites FDA visited promote dietary supplement products for treatment of diseases, including arthritis, cancer, and HIV/AIDS. CFSAN will be revisiting these sites to verify whether the website operators made corrective actions. FDA is planning follow up as appropriate. In addition, FDA and FTC are evaluating the responses to these advisory letters and they will coordinate appropriate enforcement actions if they are necessary.

In July 1999, FDA adopted, and has since been implementing, an Internet Drug Sales Action Plan to expand and improve its activities in addressing the unlawful sale of drugs over the Internet. The illegally marketed drugs targeted by the plan include a variety of fraudulent products, including counterfeit drugs, drugs marketed with fraudulent health-related claims, and unapproved new drugs masquerading as dietary supplements. The elements of the plan include, among others:

- Public Outreach: FDA Talk Papers, articles in the FDA Consumer magazine, and information on FDA's website to help educate consumers about safely purchasing drugs online.

- Professional Outreach and Partnering: Periodic meetings with State and Federal regulatory and law enforcement bodies, consumers, health care practitioners, and industry to share information and strategize about how to address the challenges the Internet presents.

- Coordinating Activities with other State and Federal Agencies: Established cooperative working relationships with the Drug Enforcement Administration, the Federal Bureau of Investigation, FTC, U.S. Postal Service, U.S. Customs Service, and other appropriate Federal and State law enforcement agencies.

- International Cooperation: FDA and other Federal agencies must work with foreign governments to bring action against foreign-based sellers.

ENFORCEMENT ACTION – July 2000

When a problem arises with a product regulated by FDA, the Agency can take a number of actions to protect the public health. For dietary supplements, as with other products, the Agency initially works with the marketer of the product to correct the problem

voluntarily. If that fails, the Agency also can ask the marketer to recall a product, although it cannot order a recall. The Agency can also seek, through the courts, seizure of violative products and/or an injunction against firms or individuals who market violative products, and detain or refuse entry of products presented for import at U.S. ports.

The Agency's Office of Regulatory Affairs (ORA) works in close cooperation and coordination with all of FDA's Centers in enforcing the law. With regard to health fraud specific to dietary supplements, CFSAN has the lead and is responsible for the oversight of dietary supplements. The Center for Drug Evaluation and Research also has a role to play, as many of the successful cases the Agency has brought concern products purporting to be dietary supplements that were actually drugs within the meaning of the Federal Food, Drug and Cosmetic Act and that failed to meet the regulatory requirements for drugs prior to their introduction into interstate commerce.

FDA has taken several enforcement actions pertaining to ephedra or ephedrine alkaloids. In most cases, FDA took action against these products because they contained drug ingredients, because they were promoted to treat a disease, and/ or because they presented safety concerns. In fiscal year 2002, Congress appropriated $500,000 for dietary supplement enforcement efforts.

Nature's Nutrition Formula One – July 2000

FDA determined that this pre-DSHEA product, which was marketed between 1992 and 1994, as an all natural "nutritional supplement" that contained plant ingredients, was actually made with two pharmaceutical-grade chemicals, ephedrine hydrochloride and caffeine anhydrous. FDA received more than 100 reports of injuries and adverse reactions related to the product, ranging from serious and life-threatening conditions, such as irregular heartbeat, heart attack, stroke, seizures, hepatitis and psychosis, to more minor and temporary conditions such as dizziness, headache and gastrointestinal distress. At least one death was associated with the use of this product.

This case was developed by the alerts provided from the adverse event reports, by ORA's field staff, and by the work of FDA's Office of Criminal Investigation (OCI) with DOJ. As a result, the government launched a criminal prosecution against the company and its president.

On July 7, 2000, a Federal judge sentenced its president to 21 months in jail and fined him and his corporation $4.7 million. In his plea agreement, the company admitted it labeled Formula One as "all natural" but spiked the product with synthetic ephedrine hydrochloride and caffeine anhydrous. It also admitted that the product's labeling failed to disclose the use of the chemicals on the list of ingredients, and that he and his employees had misled FDA investigators and hindered inspections of Chemins. The sentence marked the culmination of a three-year investigation.

E'OLA International, Inc. – April 2002

At the request of FDA, U.S. Marshals seized unapproved drug products from Biogenics Inc., of St. George, Utah, doing business as E'OLA International, and at its contract manufacturer, Nature's Energy, Inc., of Pleasant Grove, Utah. About 140,000 bottles of AMP II Pro Drops valued at $2.8 million were seized, along with the bulk ephedrine hydrochloride (HCl) used in its manufacture. Although the finished products contained a drug, ephedrine HCl, they were labeled as dietary supplements for use in weight loss. The products, however, do not meet the definition of a dietary supplement because ephedrine HCl is not a dietary ingredient under the Act. FDA inspections of E'OLA revealed that the firm purchased raw materials and ephedrine HCl, directed other firms produce AMP II Pro Drops on contract, and then had them ship the finished product back to E'OLA for distribution.

Ephedrine HCl has been approved as a drug by FDA since 1948, and therefore, cannot be legally marketed as a dietary supplement. In addition, E'OLA marketed AMP II Pro Drops as a treatment for obesity. Dietary supplements cannot be marketed to treat obesity, a disease. Products marketed to treat disease are drugs. The AMP II Pro Drops were also misbranded because their labeling failed to bear adequate directions for use as is required of all drug products.

In April 2002, a United States District Court Judge signed a Consent Decree of Permanent Injunction that prohibited E'OLA from holding, manufacturing, processing, packing, labeling, promoting, or distributing AMP II Pro Drops or any similar product containing or purporting to contain ephedrine HCl or any synthetic ephedrine alkaloid. Under the decree, E'OLA was also required to destroy the seized articles at its own expense under the supervision of an HHS representative.

Additional FDA Actions

FDA is still awaiting the scientific review from the RAND study, so we can better understand the safety and efficacy of ephedrine alkaloids. In the meantime, FDA is taking the following steps:

Good Manufacturing Practices (GMPs) – October 2002

There is broad public support for dietary supplements GMPs to enhance public confidence in these products. As a preventative measure, DSHEA grants FDA explicit authority to establish GMP regulations for dietary supplements. Such regulations are critical to assuring quality, purity, and consistency in dietary supplement products. FDA has made the publication of a GMP proposed rule a high priority. After the publication, we will conduct an outreach program of the proposed rule. On Friday, October 4, 2002, the proposed rule was forwarded to Office of Management and Budget for a 90 day review.

Aggressive Enforcement of Synthetic Products

In addition to our prior efforts on synthetic ephedrine alkaloid enforcement, FDA is interested in conducting a systematic pharmacological analysis of ephedra products on the market to assess the need for further enforcement against products that contain synthetic ephedrine alkaloids.

Increased Enforcement of Illegal Ephedrine – June 14, 2002

FDA is aggressively pursuing the illegal marketing of non-herbal synthetic ephedrine alkaloid products. As part of these efforts, FDA sent six warning letters to firms unlawfully selling non-herbal ephedrine alkaloid-containing products over the Internet. Six letters went to manufacturers of products that contain the drug ephedrine or norephedrine hydrochloride labeled as dietary supplements for use in weight loss, suppression of appetite, enhanced libido, and the like. These products violate the law because they are not legal dietary supplements and are illegal drugs. Also, FDA warned another company for illegally promoting its herbal ephedra product as an alternative to street drugs.

Warning Labels

Secretary Thompson and I are very concerned about the safety of ephedra. The Secretary has requested that FDA evaluate mandatory warning labels as quickly as possible to properly alert the public regarding potential risks associated with the consumption of dietary supplements containing ephedrine alkaloids.

Yellow Jackets

Mr. Chairman, thank you for calling to Secretary Thompson's attention the death of the 16 year old boy who ingested the product, Yellow Jackets, in your letter of October 2, 2002. I have referred the matter to our enforcement personnel who have identified a distributor in the Netherlands who is making claims that are illegal under U.S. law. The website indicates that the product is intended to be used as an alternative to illicit street drugs, and is, therefore, being illegally marketed in this country. I know this comes as little comfort to the boy's family who have suffered such a tragic loss, but, yesterday, FDA issued a Cyber letter to the foreign distributor and we alerted consumers that these products present health risks. We are working closely with law enforcement officials in the Netherlands and the U.S. Customs Service to block entry of Yellow Jackets into this country by placing this product on Import Alert.

CONCLUSION

FDA will continue to work collaboratively with other governmental agencies, academia, health professionals, industry, and the Congress so that we all can be assured that we are protecting the American consumer with regard to the safety of dietary supplements. In support of that effort, the Agency firmly believes that its Dietary Supplement Strategic Plan will provide the necessary blueprint, for a comprehensive program that will implement the additional regulatory responsibilities required of FDA by DSHEA. The Agency is committed to utilizing all resources in a manner consistent with the goals and activities delineated in DSHEA in order to achieve success.

Mr. Chairman, thank you for this opportunity to testify. I am happy to answer your questions.

CONGRESSWOMAN SUSAN DAVIS
Statement for the Record
to the
Oversight of Government Management, Restructuring and
the District of Columbia Subcommittee
Senate Government Affairs Committee
United States Senate

Ephedra: Who is Protecting American Consumers?
October 8, 2002

Walk into any neighborhood drug store or discount store and you will find yourself surrounded by a variety of diet aids and athletic performance enhancers. Labels tout promises of safe and easy weight loss or increased muscle gain, appealing to the hopes and goals of many adults and a growing number of teens. Many of these supplements contain ephedra, also commonly listed as ma-huang or ephedrine alkaloids. Sadly, many consumers, including some of my own constituents, have experienced adverse reactions after using ephedra-based supplements.

Promoted to accelerate one's metabolism, ephedra works by constricting blood vessels, raising blood pressure and causing the heart to beat more rapidly. Supplements containing this ingredient have been associated with cardiovascular events, increased risk of heat injury, depression, agitation, heart attack, stroke and even death. These severe effects demand that increasing public awareness be a priority, especially because the average customer profile includes minors. Today's hearing on ephedra and consumer safety is an important step in bringing more attention to this public health issue.

My interest in dietary supplements containing ephedra stems back to my tenure as a California State Assemblywoman. Numerous constituents contacted me and shared their personal accounts of side effects after taking dietary supplements with this substance. Many expressed remorse and said they would have thought twice about taking ephedra products if they had known about the possible risks. I introduced legislation in the California State Assembly to address these important issues, and I am pleased to report that Governor Gray Davis recently signed a very similar bill into law.

The prevalence of these side effects can only increase as the dietary supplement industry grows. According to the Nutrition Business Journal, Americans will spend $18.5 billion dollars on supplements in 2002 and reach almost $21 billion dollars in 2005. This is no

surprise since potential customers can easily obtain supplements from nutrition shops, discount stores, and retailers advertising in magazines, the Internet or television commercials. In contrast, finding accurate information about the risks and benefits associated with supplement use is difficult. Obtaining adverse event reports of side effects, injuries or deaths from the dietary supplement industry has been an ongoing challenge for the Food and Drug Administration.

The recent release of over 13,000 product-related adverse event reports from Metabolife, a San Diego-based company, underscores the need for greater communication. Of the reports, nearly 2,000 involved significant adverse reactions such as seizures, heart attacks, and even death. Unfortunately, a majority of the documents were handwritten, sometimes illegible and contained incomplete information. In order for the FDA to provide consumers with the information they need about the benefits and risks of these products, changes in the laws governing adverse event reporting are necessary.

Since coming to Congress, I have been working to address some of these pressing concerns on a national level. I have introduced two bills in the House of Representatives that will strike a balance between allowing the industry access to the marketplace while giving consumers the information they need to make informed decisions about the safety, efficacy and contents of dietary supplements.

The Dietary Supplement Information Act, H.R. 3065, would require dietary supplement companies to forward all adverse event reports to the FDA within 15 days of receiving those reports. It also requires dietary supplement companies to register with the FDA and allows for the development of regulations for product registration, such as listing ingredients and quantities. Under H.R. 3065, supplement companies would be required to submit their adverse event reports to the FDA as they received them.

Providing the FDA with access to these critical reports benefits both consumers and the supplement industry. The FDA needs the adverse event reports in order to determine if ephedra is the true cause of these deadly side effects. Without scientific scrutiny of all adverse event reports, we will never know if there is a safe dosage of ephedrine, or if there is a certain subset of our population that is especially vulnerable to serious side effects.

The Ephedrine Alkaloid Consumer Protection Act, H.R. 3066, continues the effort that I began at the state level to require warning labels on dietary supplements containing ephedra. The label would list the possible risks involved in taking ephedrine alkaloids, and would include the FDA's MedWatch phone number, which encourages consumers experiencing side effects to report them directly to the FDA. Consumers who contact MedWatch will reach qualified personnel trained to thoroughly collect and review relevant information and produce a complete report of the adverse incident. More importantly, H.R. 3066 would ban the sale of ephedrine supplements to children under the age of 18. To ensure that this provision is enforced, the bill requires products containing ephedra be kept behind store counters so that sales personnel are responsible for distributing the products consistent with the age restriction.

Momentum is clearly growing for improving consumer safety regarding ephedra, illustrated by the growing number of organizations that are addressing the issue on their own. The National Football League has been the latest sports organization, along with the International Olympic Committee and the National Collegiate Athletic Association, to ban the use of ephedra.

Many young athletes emulate the practices of their professional sport heroes. Their developing bodies are especially susceptible to the effects of stimulants. If ephedra is not appropriate for the pros, then it should not be appropriate for Pop Warner.

The legislation recently signed by Governor Davis continues this issue's momentum. The new California law bans the sale of ephedra-based dietary supplements to minors, and requires that product labels include warning messages and the posting of the FDA's Medwatch number so that consumers can easily report health problems associated with taking ephedra.

In closing, I want to thank Senator Durbin for holding this important hearing today. By providing an open forum where we can discuss the issue of dietary supplements, Senator Durbin is truly helping American consumers make more informed decisions. Consumers have a right to know what they are putting into their bodies, but current law is preventing the FDA from being able to collect and distribute accurate information about dietary supplements. A change in the current law is critically needed. My legislation is a common-sense approach to giving the FDA the authority to regulate the industry, allowing the industry free-market access, increasing the flow of information to the consumer, and protecting our children. The American public deserves clear information about the benefits and risks of supplements.

Health Canada / Santé Canada
Health Products and Food Branch / Direction générale des produits de santé et des aliments

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US Senator Richard J. Durbin
Chairman
Senate Subcommittee on Oversight of
Government Management, Restructuring
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20510

Dear Senator Durbin:

This refers to your request for an official from Health Canada to participate in the hearings of the Senate Subcommittee on Government Oversight on the issue of consumer safety and dietary supplements, particularly as it pertains to ephedra or ephedrine.

We regret that we could not delegate a representative from Health Canada with the expertise on the safety issues surrounding the use of products containing ephedra or ephedrine to participate in the hearings in question. As an alternative, we are forwarding to you a summary of the regulatory status of products containing ephedra or ephedrine in Canada, as well as copies of material relevant to the actions recently taken by Health Canada on this issue. These advisories are also posted on our website at www.hc-sc.gc.ca/english/protection/warnings.html.

Health Canada has taken regulatory action on other natural health products (termed as dietary supplements under the DSHEA legislation in your country) marketed in Canada over the last few years. For example, products containing aristolochia have been removed from the market one year ago, and kava containing products have recently

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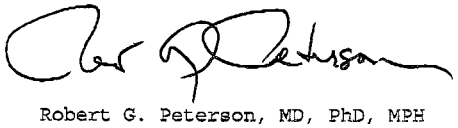
been recalled from the market. Should you require more specific information regarding these regulatory actions or other regulatory actions affecting the product category in question, we would be pleased to respond to your specific requests.

I trust that this material will be useful to you.

Yours sincerely,



Robert G. Peterson, MD, PhD, MPH
Director General

Attachments

REGULATORY STATUS OF PRODUCTS CONTAINING EPHEDRA OR EPHEDRINE IN CANADA

Over the last few years, Adverse Reaction Reports associated with the use of products containing *Ephedra* or ephedrine led Health Canada to review the regulatory status of the products in question. Many products containing these ingredients have been sold in Canada over-the-counter (OTC) for several years and no recent assessment of the risks and benefits of such products was available.

Products containing ephedrine had been used in the past as asthma treatments, but they have been replaced for this indication by newer therapies. Further, the treatment of asthma is considered to require close supervision by health care providers rather than self-treatment with OTC medications.

In June 2001, Health Canada issued an Advisory recommending that consumers not use certain products containing *Ephedra* or ephedrine in view of reports of serious adverse reactions, including deaths, being received worldwide (copy of Advisory attached). The product categories of particular concern included those that contained a stimulant ingredient in addition to *Ephedra* or ephedrine, those recommended for weight loss, body building or as energy booster, as well as those recommending an intake exceeding 8 mg per single dose or 32 mg per day of ephedrine or ephedrine alkaloids.

The use of products containing ephedrine alkaloids in combination with other stimulants, such as caffeine, has not been established to be safe.

The use of products containing ephedrine alkaloids for indications such as weight loss, increased exercise endurance and muscle building has not been established as effective, is likely to occur at doses higher than those considered safe, and to be taken for periods of time for which safety has not been established.

Following the release of this Advisory, Health Canada pursued its evaluation of the available data to determine if the risks being reported warranted regulatory action.

The evaluation of available data and information led to the release in January 2002 of a further Advisory announcing the recall of various types of *Ephedra* or ephedrine containing product categories sold without marketing authorization. In addition to the recall, Health Canada requested that manufacturers of products with prior marketing authorization provide evidence of safety for products recommending dosages exceeding 8 mg per single dose and 32 mg per day of

ephedrine or ephedrine alkaloids equivalent. These dosage limits had been considered safe and appropriate for OTC products used as nasal decongestant by an Expert Committee evaluating nonprescription cough and cold remedies available in Canada in 1989. Under the *Food and Drugs Act and Regulations*, it is the responsibility of the product manufacturers to demonstrate the safety and efficacy of the drug products they offer for sale in Canada. The *Regulations* authorize Health Canada to request that manufacturers demonstrate that products on the market are safe, and to require that products be removed from the market if their safety cannot be established. None of the manufacturers provided sufficient or adequate data to support the higher doses and the products have been removed from the market.

The actions taken were based on the data available at the time as well as on criteria related to the application of the Precautionary Principle. Although the details of adverse reaction reports available did not permit the confirmation of a cause and effect relationship between the use of the products and the events reported, the associations between the use of the products and the adverse events were considered to be a probable or a partial cause of the events, and therefore warranted regulatory action.

Products containing ephedrine or *Ephedra* recommended for use as nasal decongestants at doses not exceeding 8 mg per single dose and 32 mg per day of ephedrine equivalent, and to be used for no more than seven days may remain on the market at this time. Should a manufacturer wish to obtain authorization to sell a product for the treatment of a condition other than nasal decongestion and/or at higher doses, they would be required to submit an application with substantial evidence of safety, efficacy and quality to support the indication. If the indication was for treatment of asthma and the product was found to be safe and effective and of high quality, it would be regulated as a prescription only drug.

In Canada, the *Regulations* under the *Food and Drugs Act* require all drug products be authorized for sale by the federal health department prior to sale. The authorization is given in the form of a Drug Identification Number (DIN) which is required to appear on the main panel of the drug product labels. Under the current legislation, all products intended to be ingested are regulated as either food or drugs.

The creation of a third category of products, to be named "natural health products", was announced in 1999. Proposed *Natural Health Products Regulations* are expected to be in place in 2003 and will cover the manufacturing and sale of herbs, vitamins, minerals, neutraceuticals, etc., which are considered safe for over the counter use Natural health products will be regulated as a subset of drugs under the *Food and Drugs Act* but with a separate set of regulations. They will also require a pre-market assessment for safety, efficacy and quality prior to being authorized for sale in Canada. Levels of evidence required will vary depending on the nature of the claim, but will not be limited to double blind clinical trials.

Pending the implementation of the Natural Health Products Regulations, interim measures are applied to products that fall into this category. These measures, while they do not exempt products currently considered to be drugs from the requirements of pre-market authorization, provide for minimal enforcement activity should the regulatory requirements not be met. Consequently, products containing *Ephedra* may remain on the market without pre-market authorization, provided that they do not contain another stimulant, are not recommended for the conditions listed under the recall provisions above, and are not recommended for dosages or duration of use exceeding those mentioned above for ephedrine products that may continue to be marketed.

Health Canada will continue to monitor and assess the benefits and risks of products containing ephedra, ephedrine and related compounds that may currently remain on the market, and may further consider its regulatory action, should this be warranted by new evidence.

(Attachment)

January 2002

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Information

Ephedra/ephedrine - Frequently Asked Questions

1. What is *Ephedra*?
Ephedra refers to several related species of herbs that commonly grow in desert areas. It is best known as a botanical source of the alkaloids ephedrine, pseudoephedrine and others. *Ephedra* species also contain many other constituents. *Ephedra sinica*, whose Chinese name is Ma Huang, has been used in recent years in products marketed for weight loss, body building and increased energy.

2. What is ephedrine?
Ephedrine is a chemical derivative of the herb *Ephedra sinica* and several other species of *Ephedra*, and was first isolated and used pharmaceutically about 100 years ago. It stimulates the central nervous and the cardiovascular systems, and causes the lung bronchi to dilate. Products containing ephedrine may use the compound extracted from *Ephedra* or be produced synthetically.

3. What is the problem with *Ephedra*/ephedrine? Why is Health Canada requesting a recall?
Health Canada currently authorizes the sale of oral products containing recommended or low dosages of *Ephedra*/ephedrine for use for short periods of time as nasal decongestants. These products carry an 8 digit Drug Identification Number (DIN), which indicates they have been approved by Health Canada. There are also products that contain *Ephedra* for use as traditional medicines.

However, Health Canada is aware that many unapproved products are sold for a variety of uses including weight loss, increased energy, body-building and euphoria. These unapproved products are usually combination products containing *Ephedra*/ephedrine with stimulants such as caffeine.

A health advisory was issued by Health Canada in June of last year, advising Canadians not to use products containing *Ephedra*/ephedrine with caffeine and other stimulants for purposes of weight loss, body building or increased energy. At the time of that advisory, 60 adverse events had been reported in Canada related to the use of *Ephedra*/ephedrine. Most such reactions involved the use or overuse of combination products, which combine *Ephedra*/ephedrine with caffeine or other substances that increase its action. Since the last advisory, a product that combined large doses of ephedrine with caffeine has been reported as a contributing factor in one death.

At the time of the last advisory, Health Canada had initiated a thorough risk assessment, and concluded that the following *Ephedra*/ephedrine products pose a health risk, and should be removed from the market:

- *Ephedra*/ephedrine products having a dose unit of more than 8 mg ephedrine or with a label recommending more than 8 mg/dose or 32 mg/day;
- combination products containing *Ephedra*/ephedrine together with stimulants (e.g. caffeine or other ingredients that would enhance the activity of *Ephedra*/ephedrine);
- *Ephedra*/ephedrine products with labelled or implied claims for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects.

4. Are there groups that are particularly at high risk? What are the side effects?
Products containing ephedrine are contra-indicated in heart disease, hypertension, thyroid disease, diabetes, enlarged prostate, anxiety and restlessness, glaucoma and pheochromocytoma. *Ephedra*/ephedrine aggravates these conditions and therefore should not be used except if recommended by and under the surveillance of a health care professional. It should also not be used during pregnancy and lactation.

Adverse effects of ephedrine can include dizziness, headache, decreased appetite, anxiety, restlessness or nervousness, gastrointestinal distress, irregular heartbeat, tachycardia, insomnia, flushing, sweating, hypertension, stroke, seizures, psychosis and death.

As well, due to the stimulant and euphoric properties of *Ephedra*/ephedrine, certain segments of the population are more likely to abuse these products, increasing the risk to their health.

5. How can a consumer identify these products?
Although there are potentially hundreds of these products on the shelves, which makes them difficult to identify by product name, consumers are advised to check the label. Things in particular to watch out for:

- Check for a Drug Identification Number. If the product is making a health claim, it should have one. DINs identify the product as having been approved by Health Canada. *Ephedra*/ephedrine products without DINs have not been assessed for safety by Health Canada, and as such their safety cannot be assured.
- Consumers are particularly advised to check the label for products that combine *Ephedra*/ephedrine with stimulants such as caffeine. A list of some of the herbs or plants that contain caffeine is being provided to consumers.
- Products that are marketed for appetite suppression, weight-loss, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects may contain *Ephedra*/ephedrine and should be treated with some suspicion. These products have not been assessed by Health Canada and have no assurance of content, safety or effectiveness.
- If you are taking a product that contains *Ephedra*/ephedrine, and are not sure whether the product meets the recommended standard of 8mg/a dose, 32 mg/day for ephedrine, consult your pharmacist.

6. Will all products labeled to contain *Ephedra*/ephedrine be taken off the

shelves?
No. Commercial Ephedra/ephedrine products being sold as nasal decongestants and having a dose equal to or under the recommended dosage of 8mg/a dose or 32mg/day will continue to be available. Products containing *Ephedra* which are marketed for traditional use according to the combinations and dosages described in texts pertaining to traditional medicine, will also continue to be available, provided they do not contain caffeine and that the ephedrine content does not exceed the 8 mg/a dose to a maximum of 32 mg/day.

As well, the recall does not affect Ephedra/ephedrine products that are being dispensed by practitioners who are dispensing/compounding the drug for individual patients.

7. Why take action now?
Health Canada issued a public advisory regarding these products in 1997 and in June 2001 cautioning Canadians of the possible adverse health effects these unapproved products may pose. At the time of the last advisory (June 2001), Health Canada had initiated a risk assessment to determine the risk to health of these products. The assessment concluded these products pose a serious risk to health, and now Health Canada is removing them from the market.

8. What compliance activities are being done?
Health Canada has / will:

- issued a Public Advisory to inform Canadian consumers of the Class 1 risk to health posed by unapproved *Ephedra*/ephedrine products for some population groups with pre-existing conditions, such as hypertension, diabetes, heart disease, etc. A Class I risk to health is defined as a situation where there is a reasonable probability that the use of, or exposure to, a product will cause serious adverse health consequences or death;
- issued a Customs Lookout for the products in question to ensure that they are stopped at the border and not imported into Canada;
- issued a Letter to Canadian manufacturers, distributors and importers to advise them of the recall, and request that they discontinue the sale of these products at all levels of the market, including retail;
- issued letters to manufacturers of *Ephedra*/ephedrine products that carry DINs and provide doses greater than 8 mg/dose or greater than 32 mg/day, requesting that they provide safety data to support these higher doses in their products;
- communicated its actions to other international regulatory agencies regarding these products as per information sharing agreements, and to other stakeholders as appropriate;
- follow-up with importers, manufacturers and retailers to assess the effectiveness of the recall for these products; and
- conduct a random market survey within 6 months of the recall to determine whether these products have found their way back onto the Canadian market. Non-compliant products will be removed from the shelves.

9. How did so many unapproved products get on the market?
Natural health products are currently regulated as either a food or a drug, and as such, have been dealt with on a case by case basis. New regulations are

being proposed which will enable better regulation of natural health products such as these.

It should be noted that these products are often clandestinely imported into Canada. Health Canada initiated a risk assessment in June to determine the full scope of the risk posed by these products. To help mitigate risks to consumers in the meantime, Health Canada issued a public advisory warning consumers not to use these products, as a precautionary measure, while the risk assessment could be completed.

10. Since these products are so widespread, how can you be sure all products in question will be removed?
Health Canada has implemented the following actions to remove as many as possible:

- issued a letter to manufacturers, distributors and importers to inform them of the recall, requesting that they remove these products from sale.
- issued a letter to as many associations as possible including the Canadian Trucker's Association, the Canadian Consumers' Association, fitness centres, gyms, the College of Physicians and Surgeons, Canadian Association of Family Physicians, among others to inform them of the recall.
- issued an indefinite Customs Lookout for these products to ensure they do not enter into Canada.

This is also a matter of supply and demand, and consumers have a role to play in keeping these products off the shelves. Health Canada has in the past (in 1997 and in June of this year) issued two advisories, advising the public not to consume these products, but a continuing demand for these products has ensured they remain on the shelves. Canadians could also contribute to this initiative in ceasing to purchase such products and eliminate the demand.

Health Canada inspectors will undertake a random market survey in approximately 6 months following the recall of these products to determine how successful the recall was, and if further actions need to be taken.

11. If a consumer has concerns about a product they find on the shelf, who can they contact?
Consumers can direct their questions and complaints to the Health Products and Food Branch Inspectorate Operational Centre closest to them (please see list below).

HEALTH PRODUCTS AND FOOD BRANCH INSPECTORATE OPERATIONAL CENTRES

Atlantic	**Manitoba and Saskatchewan**
Annette Daley Suite 1625, 1505 Barrington St. Halifax, Nova Scotia B3J 3Y6 Tel: (902) 426-5350 Fax: (902) 426-6676	Robert Scales 510 Lagimodière Blvd. Winnipeg, Manitoba R2J 3Y1 Tel: (204) 983-5453 Fax: (204) 984-2155
Québec	**Western**
Alain Bérubé	Dennis Shelley

1001 ouest, rue St-Laurent
Longueil, Québec
J4K 1C7
Tel: (450) 646-1353, ext. 232
Fax: (450) 928-4455

3155 Willingdon Green
Burnaby, British Columbia
V5G 4P2
Tel: (604) 666-3704
Fax: (604) 666-3149

Ontario

Jean-Marc Charron
2301 Midland Avenue
Scarborough, Ontario
M1P 4R7
Tel: (416) 973-1466
Fax: (416) 973-1954

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2001-67
June 14, 2001

Advisory

Advisory not to use products containing Ephedra or ephedrine

OTTAWA - Health Canada is warning consumers not to use products containing the herb Ephedra, either alone or in combination with caffeine and other stimulants, for purposes of weight loss, body building or increased energy. Products containing Ephedra or ephedrine in combination with caffeine and other stimulants are of particular concern, since ephedrine may cause serious, possibly fatal, adverse effects in the body when combined with these ingredients.

Ephedra is a botanical source of the drug ephedrine, and is used in traditional and cultural medicines. It is authorized by Health Canada for use as a nasal decongestant in over-the-counter cold products only. All such products carry a Drug Identification Number (DIN) and should be used only as directed, for short periods of time.

However, Health Canada is aware that many ephedrine-containing preparations that are not approved for sale in Canada are being used by Canadians. They most often contain a combination of Ephedra and caffeine or some other stimulant. These Ephedra/stimulant combinations are not commonly promoted in the practice of traditional and cultural medicine. Instead, they are frequently imported for personal use, or sold in various retail establishments such as fitness centres and health food stores and marketed as diet aids, or energy boosters.

Ingredient panels on these products may list ma huang, Chinese Ephedra, ma huang extract, Ephedra, Ephedra Sinica, Ephedra extract, Ephedra herb powder, Sida Cordifolia or epitonin, all of which indicate a source of ephedrine. Sources of caffeine or other stimulants in these products may include: green tea, guarana, yerba mate, cola nut and yohimbe.

A review of a U.S. Food and Drug Administration database of adverse event reports collected between June 1, 1997, and March 31, 1999, identified 10 cases resulting in death and 13 cases resulting in permanent impairment that were considered to be possibly, probably, or definitely related to dietary supplements containing ephedra alkaloids. In Canada, a total of 60 adverse event reports have been received by Health Canada related to Ephedra or ephedrine, alone or in combination with other products, previous to October 2000. This total includes two deaths, both suicides, which may or may not have been directly associated with the use of these products. Reported adverse events range from episodes that may indicate the potential for more serious effects, such as dizziness, tremors, headaches and irregularities in heart rate, to seizures, psychosis, heart attacks, and stroke.

Health Canada advises all individuals who may have used these products for weight loss or increased energy to stop consuming them and consult their health care practitioner if they have experienced any adverse effects from taking the product.

Media inquiries:
Ryan Baker
Health Canada
(613) 941-8189

Last Updated: 2001-06-14 ▲ Important Notices

1997-38
June 5, 1997

Warning

Warning not to use products containing the herb EPHEDRA, also known as MA HUANG

OTTAWA - Health Canada is warning consumers not to use products containing the herb EPHEDRA, also known as MA HUANG, unless the product label carries a Drug Identification Number (DIN). The DIN is an eight digit number which appears on the front of the product label, preceded by the letters DIN or GP.

Health Canada has received notice that the US government is expected to announce shortly a number of measures to curtail the sale of preparations containing ephedrine alkaloids.

Preparations containing this herb or its active constituent have caused close to 20 deaths in the US over the last few years and hundreds of adverse reactions. In Canada, products containing ephedrine are regulated as drugs and are only authorized for sale by Health Canada after a review of the product's safety and efficacy. Preparations containing ephedrine are safe and effective when used for the authorized conditions. At this time, the only approved non-prescription use is in a nasal decongestant, and dosage directions and precautions should be strictly followed. Such products are only recommended for use for short periods of time. If in doubt, a doctor or pharmacist should be consulted prior to use.

Health Canada is aware that many ephedrine-containing preparations not approved for sale in Canada are used by Canadians. They are frequently imported for personal use, or clandestinely sold in establishments such as fitness centres for a variety of purposes, including weight loss, increased energy and body building. Ingredient panels on these products may list ma huang, Chinese ephedra, ma huang extract, ephedra, Ephedra sinica, ephedra extract, ephedra herb powder, or epitonin, all of which indicate a source of ephedrine.

These products pose the same potential for adverse effects as those seen in the US. Reported adverse events range from episodes that may indicate the potential for more serious effects, for example, dizziness, tremors, headaches, and irregularities in heart rate to seizures, heart attacks, strokes, and death.

Health Canada urges all individuals who may have these products to stop consuming them and to consult their health care professionals immediately if they experience any adverse effects.

Information:

Micheline Ho
Health Canada
(613) 954-4922
Pager: (613) 598-9034

Public Inquiries:
(613) 957-2991

Last Updated: 1997-06-05 ▲ Important Notices

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2002-01
January 9, 2002

Advisory

Health Canada requests recall of certain products containing Ephedra/ephedrine

OTTAWA- Health Canada is requesting a recall from the market of certain products containing *Ephedra*/ephedrine after a risk assessment concluded that these products pose a serious risk to health. Adverse events including stroke, heart attacks, heart rate irregularities, seizures, psychoses and deaths have been reported in association with the use of some products containing *Ephedra*/ephedrine. Ephedra refers to several related species of herbs. *Ephedrine* is one of many chemical derivatives of this herb.

This voluntary recall deals with products that are marketed without approval. These include:

- *Ephedra*/ephedrine products having a dose unit of more than 8 mg of ephedrine or with a label recommending more than 8 mg/dose or 32 mg/day and/or are labelled or implied for use exceeding seven days;
- all combination products containing *Ephedra*/ephedrine together with stimulants (e.g. caffeine) and other ingredients which might increase the effect of Ephedra/ephedrine in the body. A full table of ingredients containing caffeine is attached to this advisory;
- *Ephedra*/ephedrine products with labelled or implied claims for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects.

Health Canada advises those Canadians who may be consuming these products to stop using them, and return them to their points of sale. Canadians suffering from heart conditions, high blood pressure and diabetes are among those particularly at risk.

Currently, the maximum allowable dosages for *Ephedra*/ephedrine in products is 8 mg ephedrine/single dose or 32mg ephedrine/day. Products containing *Ephedra* which are marketed for traditional medicine, will continue to be available, provided they do not contain caffeine and that the ephedrine content does not exceed 8 mg/dose to a maximum of 32 mg/day.

If a consumer has concerns about a product with a Drug Identification Number (DIN), and is not sure if the recommended dosage exceeds the 32 mg ephedrine/day dose limit, they should consult with their pharmacist. Consumers who identify remaining products on the shelves can call their regional Health

Canada offices to report complaints. Their contact information is provided as an attachment.

Health Canada is issuing letters to Canadian manufacturers, distributors and importers requesting that they discontinue sale of these products and that the products be recalled from all levels of the market, including retail. A customs lookout has also been issued, to ensure that these products are not imported into Canada.

A health advisory was issued by Health Canada in June of last year, advising Canadians not to use products containing the herb *Ephedra*, in combination with caffeine and other stimulants, for purposes of weight loss, body building or increased energy. At the time of that advisory, 60 adverse events had been reported in Canada related to the use of *Ephedra*/ephedrine. Since then, a product which combined large doses of ephedrine with caffeine has been reported as a contributing factor in one death in Canada.

Health Canada will be issuing a regulatory letter to manufacturers of products which exceed this recommended dosage. Products with DINs that are being sold as nasal decongestants and have doses equal to or less than the upper limits of 8 mg ephedrine/dose and 32 mg ephedrine/day will continue to be available.

Health Canada will continue to monitor reports of adverse events associated with Ephedra/ephedrine, and will take further action if necessary. A random market survey will be undertaken within 6 months of the requested recall to determine whether these products have found their way back onto the Canadian market. Non-compliant products will be removed from the shelves.

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Media Inquiries:
Ryan Baker
Media Relations
Health Canada
(613) 941-8189

Public Inquiries:
(613) 957-2991

To report complaints, the regional contacts are:

Health Products and Food Branch Inspectorate Operational Centres

Atlantic	**Manitoba and Saskatchewan**
Annette Daley Suite 1625, 1505 Barrington St. Halifax, Nova Scotia B3J 3Y6 Tel: (902) 426-5350 Fax: (902) 423-6676	Robert Scales 510 Lagimodière Blvd. Winnipeg, Manitoba R2J 3Y1 Tel: (204) 983-5453 Fax: (204) 984-2155
Québec	**Western**
Alain Bérubé 1001 ouest, rue St-Laurent Longueil, Québec	Dennis Shelley 3155 Willingdon Green Burnaby, British Columbia

J4K 1C7
Tel: (450) 646-1353, ext. 232
Fax: (450) 928-4455

V5G 4P2
Tel: (604) 666-3704
Fax: (604) 666-3149

Ontario

Jean-Marc Charron
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Scarborough, Ontario
M1P 4R7
Tel: (416) 973-1466
Fax: (416) 973-1954

Last Updated: 2002-01-09

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January 2002

Information

What to look for

Although there are potentially hundreds of these products on the shelves, which makes them difficult to identify by product name, consumers are advised to check the label. Consumers are particularly advised to check the label for products that combine *Ephedra*/ephedrine with stimulants such as caffeine.

Herbs or Plants that contain the chemical constituent Ephedrine:

- Ephedra (ma huang): *Ephedra sinica* (Ephedrine can also come from other (but not all) *Ephedra* species such as: *Ephedra shennungiana, Ephedra gerardiana, Ephedra equisetina, Ephedra intermedia*)
- *Sida cordifolia*

Herbs or plants that contain caffeine:

- Coffee - *Coffea species*
- Green tea - *Camellia sinensis*
- Guarana - *Paullinea cupana*
- Maté - *Ilex paraguariensis*
- Cola nut (Kola nut) - *Cola nitida*, (also other species such as *C. acuminata, C. verticillata, C. anomala*)

Things in particular to watch out for:

- Check for a Drug Identification Number. If the product is making a health claim, it should have one. DINs identify the product as having been approved by Health Canada. *Ephedra*/ephedrine products without DINs have not been assessed for safety by Health Canada, and as such their safety cannot be assured.
- Products that are marketed for appetite suppression, weight-loss, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects may contain *Ephedra*/ephedrine and should be treated with some suspicion. These products have not been assessed by Health Canada and have no assurance of content, safety or effectiveness.
- If you are taking a DIN product that contains *Ephedra*, and are not sure whether the product meets the recommended standard of 8mg/a dose, 32 mg/day for ephedrine, consult your pharmacist.

DEPARTMENTAL CONSOLIDATION

OF THE

FOOD AND DRUGS ACT

AND OF THE

FOOD AND DRUG

REGULATIONS

WITH AMENDMENTS TO DECEMBER 19, 2001

●

ISSUED BY

DEPARTMENT OF HEALTH

●

AN ACT RESPECTING FOOD, DRUGS, COSMETICS AND THERAPEUTIC DEVICES

Short Title

Short Title

1. This Act may be cited as the Food and Drugs Act.

Interpretation

Definitions

2. In this Act,

"advertisement" ***«publicité» ou «annonce»***
"advertisement" includes any representation by any means whatever for the purpose of promoting directly or indirectly the sale or disposal of any food, drug, cosmetic or device;

"analyst" ***«analyste»***
"analyst" means a person designated as an analyst for the purpose of the enforcement of this Act under section 28 or under section 13 of the *Canadian Food Inspection Agency Act*;

"contraceptive device" ***«moyen...»***
"contraceptive device" means any instrument, apparatus, contrivance or substance other than a drug, that is manufactured, sold or represented for use in the prevention of conception;

"cosmetic" ***«cosmétique»***
"cosmetic" includes any substance or mixture of substances manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth, and include deodorants and perfumes;

"Department" ***«ministère»***
"Department" means the Department of Health;

"device" ***«instruments»***
"device" means any article, instrument, apparatus or contrivance, including any component, part or accessory thereof, manufactured, sold or represented for use in
(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
(b) restoring, correcting or modifying a body function or the body structure of human beings or animals,
(c) the diagnosis of pregnancy in human beings or animals, or
(d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring,
and includes a contraceptive device but does not include a drug;

"drug" ***«drogue»***
"drug" includes any substance or mixture of substances manufactured, sold or represented for use in
(a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals,
(b) restoring, correcting or modifying organic functions in human beings or animals, or
(c) disinfection in premises in which food is manufactured, prepared or kept;

"food" ***«aliment»***
"food" includes any article manufactured, sold or represented for use as food or drink for human beings, chewing gum, and any ingredient that may be mixed with food for any purpose whatever;

"inspector" ***«inspecteur»***
"inspector" means any person designated as an inspector for the purpose of the enforcement of this Act under subsection 22(1) or under section 13 of the *Canadian Food Inspection Agency Act*;

"label" ***«étiquette»***
"label" includes any legend, word or mark attached to, included in, belonging to or accompanying any food, drug, cosmetic, device or package;

"Minister" ***«Ministre»***
"Minister" means the Minister of Health;

"package" ***«emballage»***
"package" includes anything in which any food, drug, cosmetic or device is wholly or partly contained, placed or packed;

"prescribed" ***«version anglaise seulement»***
"prescribed" means prescribed by the regulations;

C.01.013. (1) Where the manufacturer of a drug is requested in writing by the Director to submit on or before a specified day evidence with respect to a drug, the manufacturer shall make no further sales of that drug after that day unless he has submitted the evidence requested.

(2) Where the Director is of the opinion that the evidence submitted by a manufacturer, pursuant to subsection (1), is not sufficient, he shall notify the manufacturer in writing that the evidence is not sufficient.

23-6-71 (3) Where, pursuant to subsection (2), a manufacturer is notified that the evidence with respect to a drug is not sufficient, he shall make no further sales of that drug unless he submits further evidence and is notified in writing by the Director that further evidence is sufficient.

(4) A reference in this section to evidence with respect to a drug means evidence to establish the safety of the drug under the conditions of use recommended and the effectiveness of the drug for the purposes recommended.

Assignment and Cancellation of Drug Identification Numbers

C.01.014. (1) No manufacturer shall sell a drug in dosage form unless a drug identification number has been assigned for that drug and the assignment of the number has not been cancelled pursuant to section C.01.014.6.

19-12-96 (2) Subsection (1) does not apply in respect of a drug listed in Schedule C to the Act, whole blood and its components, or a medicated feed as defined in section 2 of the *Feeds Regulations, 1983*.

C.01.014.1 (1) A manufacturer of a drug, a person authorized by a manufacturer or, in the case of a drug to be imported into Canada, the importer of the drug may make an application for a drug identification number for that drug

19-3-81 (2) An application under subsection (1) shall be made to the Director in writing and shall set out the following information:

(a) the name of the manufacturer of the drug as it will appear on the label;
(b) the pharmaceutical form in which the drug is to be sold;
(c) in the case of any drug other than a drug described in paragraph (d), the recommended route of administration;
(d) in the case of a drug for disinfection in premises, the types of premises for which its use is recommended;
(e) a quantitative list of the medicinal ingredients contained in the drug by their proper names or, if they have no proper names, by their common names;
20-4-93 (f) the brand name under which the drug is to be sold;
(g) whether the drug is for human use, veterinary use or disinfection in premises;
(h) the name and quantity of each colouring ingredient that is not a medicinal ingredient;
(i) the use or purpose for which the drug is recommended;
(j) the recommended dosage of the drug;
19-3-81 (k) the address of the manufacturer referred to in paragraph (a) and, where the address is outside the country, the name and address of the importer of the drug;
(l) the name and address of any individual, firm, partnership, or corporation, other than the names and addresses referred to in paragraphs (a) and (k), that will appear on the label of the drug;
(m) the written text of all labels and package inserts to be used in connection with the drug and of any further prescribing information stated to be available on request; and
(n) the name and position of the person who signed the application and the date of signature.

26-8-98 (3) In the case of a new drug, a new drug submission or an abbreviated new drug submission filed pursuant to section C.08.002 or C.08.002.1 shall be regarded as an application for a drug identification number.

C.01.014.2 (1) Subject to subsection (2), if a manufacturer or importer has provided all the information described in subsection C.01.014.1(2) or section C.08.002 or C.08.002.1, as the case may be, in respect of a drug, the Director shall issue to the manufacturer or importer a document that

26-8-98 (a) sets out
- (i) the drug identification number assigned for the drug, preceded by the letters "DIN", or
- (ii) if there are two or more brand names for the drug, the drug identification numbers assigned by the Director for the drug, each of which pertains to one of the brand names and is preceded by the letters "DIN"; and

(b) contains the information referred to in paragraphs C.01.014.1(2)(a) to (f).

(2) Where the Director believes on reasonable grounds that a product in respect of which an application referred to in section C.01.014.1 has been made
(a) is not a drug, or
(b) is a drug but that its sale would cause injury to the health of the consumer or purchaser or would be a violation of the Act or these Regulations,
he may refuse to issue the document referred to in subsection (1).

(3) Where the Director, pursuant to subsection (2), refuses to issue the document, the applicant may submit additional information and request the Director to reconsider his decision.

19-3-81 (4) On the basis of the additional information submitted pursuant to subsection (3), the Director shall reconsider the grounds on which the refusal to issue the document was made.

26-8-98 **C.01.014.3** The manufacturer or importer or person authorized by the manufacturer or importer shall, within 30 days after commencing sale of a drug, date and sign the document issued pursuant to subsection C.01.014.2(1) in respect of the drug and return the document
(a) with a confirmation that the information recorded therein is correct;
(b) indicating the date on which the drug was first sold in Canada; and
(c) accompanied by samples or facsimiles of all labels and package inserts and any further prescribing information stated to be available on request.

26-8-98 **C.01.014.4** If the information referred to in subsection C.01.014.1(2) in respect of a drug is no longer correct owing to a change in the subject matter of the information,

30-4-92 (a) in the case of a change in the subject matter of any of the information referred to in paragraphs C.01.014.1(2)(a) to (f)
- (i) that occurs prior to the sale of the drug, a new application shall be made, or
- (ii) that occurs after the sale of the drug, no further sale of the drug shall be made until a new application for a drug identification number in respect of that drug is made and a number is assigned; and

30-4-92 (b) in the case of a change in the subject matter of any of the information referred to in paragraphs C.01.014.1(2)(g) to (k)
- (i) that occurs prior to the sale of the drug, the particulars of the change shall be submitted with the return of the document referred to in section C.01.014.3, or
- (ii) that occurs after the sale of the drug, the person to whom the drug identification number in respect of that drug was issued shall, within 30 days of the change, inform the Director of the change.

C.01.014.5 Every manufacturer of a drug shall, annually before the first day of October and in a form authorized by the Director, furnish the Director with a notification signed by the manufacturer or by a person authorized to sign on his behalf, confirming that all the information previously supplied by the manufacturer with respect to that drug is correct.

C.01.014.6 (1) The Director shall cancel the assignment of a drug identification number for a drug where
(a) the person to whom the number was assigned advises that the sale or import of the drug has been discontinued;
(b) the drug is a new drug in respect of which the notice of compliance has been suspended pursuant to section C.08.006; or
(c) it has been determined that the product in respect of which the number was assigned is not a drug.

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October 8, 2002

The Honorable Richard J. Durbin
Chairman
Subcommittee on Oversight of Government
Management, Restructuring, and
The District of Columbia
United States Senate
Washington, DC 20510

RE: Response to Questions Posed in September 27, 2002 Letter to Metabolife

Dear Senator Durbin:

On behalf of my client, Metabolife International, Inc. ("Metabolife"), attached are responses to the questions you posed in your letter to Metabolife dated September 27, 2002. The attached responses are based upon my best understanding of the facts.

Sincerely,

Lanny J. Davis

Lanny J. Davis
Counsel to Metabolife International, Inc.

Enclosure

Response to Questions Posed
by the Committee on Governmental Affairs
Subcommittee on Oversight of Government Management,
Restructuring, and the District of Columbia
United States Senate
October 8, 2002

1. Please discuss the system that your company has in place to receive adverse event reports from consumers.

For purposes of clarification, there is no definition of "adverse event reports" in FDA regulations for the dietary supplement industry. There is confusion concerning whether this phrase refers to causation between use of ephedrine-containing products and the reported effects. To avoid any definitional confusion, we believe the more accurate term to describe Metabolife's records referred to herein is "call records," which are anecdotal in nature.

For years now, Metabolife has voluntarily operated a toll-free customer service line as a way to provide information to interested consumers regarding appropriate usage of the products. Eventually Metabolife's system became known as the Metabolife Health Information Line and it has been staffed for the most part by registered nurses. The Metabolife Health Information Line was not established as a means to collect consumer complaints or reported incidents. Rather, the line was a way Metabolife could provide information to interested consumers regarding appropriate product usage. Call records are therefore varied in nature, as information was written on, among other items, calendars, sticky-pads, blank paper, and established forms. The system put into place by Metabolife, consistent with its purpose, was neither intended nor designed as a means to collect consumer complaints or reported incidents. Many of these records are incomplete and inconsistent. See also our response to Question No. 6, below, regarding our support for a national mandatory reporting system.

When consumers raised a health issue that they claimed required medical attention, Metabolife's practice was for the nurses or other health information representatives to advise the caller to see his or her physician if they hadn't already. If the consumer stated that they had already consulted a physician, Metabolife's general practice was and is for the nurse or other health information representative to ask the consumer to provide medical documentation regarding the claimed issue. Metabolife would send the caller, or in some cases the caller's health care practitioner, a medical release form that would allow Metabolife to receive and review the caller's medical records. Metabolife received medical records from callers in approximately 40 - 50 instances. The records were reviewed, and a medical doctor was also generally consulted regarding the records received.

2. Please advise the subcommittee of the qualifications of the Metabolife staff who have answered the health line since your company's inception.

See our response to Question No. 1 above. Currently, the Health Information Line is staffed by 3 registered nurses.

3. Please describe the training or guidance that Metabolife provides staff who are taking consumer calls with respect to the management of symptoms.

The Health Information Line staff has been instructed to become familiar with Metabolife's products and the recommended usage of such products consistent with the product's comprehensive label instructions, scientific information including published clinical trials of ephedrine containing products, and to incorporate this information into their overall health knowledge.

4. The Subcommittee is also interested in hearing about any follow-up actions that your company has undertaken to investigate any of the serious health effects that some of your consumers report having experienced while using your product.

See response to Question No. 1 above.

5. Prior to this year, how many adverse events had Metabolife shared with the Food and Drug Administration?

Until its voluntary production this year, Metabolife has not shared its call records with the FDA. See also our answer to Question No. 6, below.

6. Why has Metabolife in the past been so adverse to sharing this information with FDA?

In the context of litigation, Metabolife considered inappropriate FDA's efforts to obtain the call records in one lawsuit in which there was a court-ordered confidentiality agreement which applied to both plaintiff and Metabolife. As the court stated in its ruling upholding this confidentiality order:

> The FDA has a statutory obligation to protect the health of the general public through the regulation of products intended for human consumption. The confidentiality agreement in this case, however, has no legal relevance to the investigatory duties of the FDA. If consumer complaints were imperative to the FDA's duties, then Congress would have provided the FDA with the power to obtain such information. Indeed, Congress expressly provided the FDA with the ability to obtain consumer complaints regarding prescription drugs, but withheld this authority in regards to dietary supplements. Additionally, the GAO report (citation omitted) criticizes the FDA for its dependence upon consumer complaints in its proposed rules pertaining to dietary supplements. There is no evidence to support a finding that the FDA's interest is prejudiced or injuriously affected by the confidentiality agreement.

Having said that, Metabolife retained three experts to evaluate these call records in preparation for disclosure of these records publicly with the only exception being protecting the individual identities and personal information of the callers because of legal and other privacy obligations. As you know, subject to those privacy considerations, all of these records were turned over to your staff and the FDA – along with the reports of the three experts.

Given that there is no law or regulation requiring dietary supplement companies to report anecdotal call records, Metabolife has been under no obligation to do so. To repeat, we did so voluntarily – because we believed it might assist in the crafting of a nationally imposed mandatory reporting system, applicable to dietary supplement companies, administered by the FDA and if necessary by Congressional action. We look forward to working with FDA and Congress to achieve that objective.

7. **Your company has now turned over 14,700 adverse event reports to FDA, but they are in a format that precludes the FDA from performing any follow-up because contact information is withheld from the agency. When other companies provide FDA with adverse event reports, they do so in unredacted format. Why is Metabolife resisting providing the agency with information in a form that would allow for appropriate investigation?**

As outlined in our August 15, 2002 letter to Secretary Thompson, we are willing to try to work out some basis for providing personal information regarding our consumers consistent with privacy and other possible privilege issues. At present, the format of the production is dictated by privacy considerations and laws that we believe protect callers from public disclosure of their private information. We have indicated in our letter to Senator Durbin dated August 29, 2002, that we are prepared to provide this unredacted information as long as we obtain assurance that Federal and state privacy laws and considerations would not be violated.

See also our response to Question No. 6 above.

8. **How many personal injury cases have been filed against Metabolife? How many consumers do these cases represent? How have these cases been disposed of? How many have been settled? How many are outstanding? What is the total dollar amount that Metabolife has paid out or agreed to pay out in settlements to those claiming to have been injured by Metabolife's product? Of the cases settled, how many are sealed and thus unknown to the public?**

Over the years, there have been approximately 145 personal injury cases filed against Metabolife in State Superior and Federal District Courts. To the best of our knowledge, these cases represent approximately 160 consumers (not including several cases with undefined groups of plaintiffs). Of these cases, approximately 9 have been dismissed, one was granted summary judgment, approximately 29 have been resolved, and there are approximately 100 active cases.

We are not able to disclose the terms of individual settlement agreements because we are bound by confidentiality obligations entered into by the respective plaintiff and Metabolife, many of which were requested by either the plaintiff or insurance companies. However, we can state that

over the years approximately five million dollars has been paid in personal injury cases mostly by insurance carriers.

9. What research has your company done to evaluate the safety of its product?

To date, we are aware of over 30 reports and studies supporting the safety and/or efficacy of products that contain ephedrine alkaloids - and we believe Metabolife 356® offers consumers a safe, effective way to satisfy their weight-loss objectives. In addition to relying upon opinions of world-renowned experts, Metabolife has conducted extensive scientific literature review, commissioned laboratory tests, and has funded clinical studies. The published safety and/or efficacy clinical trials funded in all or in part by Metabolife include:

- Harry Gwirtsman, M.D., An Ephedrine, Caffeine & Chromium Compound Acutely Increases Energy Expenditure in Healthy Obese Adults, 7 (1 Supp.) Program Abstracts, NAASO Annual Meeting (Nov. 1999) (abstract).

- Carol N. Boozer, et al., An Herbal Supplement Containing Ma Huang-Guarana for Weight Loss: A Randomized, Double-Blind Trial, 25 Int'l Journal of Obesity 316 (2001).

- Carol N. Boozer, et al., Herbal Ephedra/Caffeine for Weight Loss: A 6-Month Randomized Safety and Efficacy Trial, 26 Int'l Journal of Obesity 593 (2002).

10. Does your company support a ban on sale of ephedra-containing products to minors?

Yes.

11. Please tell the committee the medical conditions a consumer might have that would make the consumer a poor candidate for an ephedra-containing product?

The Metabolife 356® label clearly states that women who are pregnant or nursing should not take the product.

In addition, the Metabolife 356® label clearly advises consumers who have, or have a family history of certain conditions such as heart disease, thyroid disease, diabetes, high blood pressure, recurrent headaches, depression, any psychiatric condition, glaucoma, difficulty urinating, enlarged prostate, seizure disorder, are using any prescription drug, a Monoamine Oxidase Inhibitor (MAOI) or any other dietary supplement, prescription drug or over-the-counter drug containing ephedrine, pseudoephedrine, or phenylpropanolanine (ingredients found in certain allergy, asthma, cough/cold and weight loss products) to consult with their physician or health care professional before taking the product.

12. Does your company believe that ephedra-containing products should only be taken under the supervision of a doctor?

As the Metabolife 356® label states, we advise consumers to consult with a physician or licensed health care professional if they meet the criteria identified on the label.

13. What other measure would your company support to provide greater safety to consumers of ephedra-containing products?

- Ban on marketing of ephedra-containing products as illicit drugs
- Ban on sale to minors
- Ban on use of synthetic ephedrine alkaloids in dietary supplements
- Good manufacturing practices (GMPs) - Including a requirement that manufacturers of dietary supplements implement quality assurance programs, such as the batch-testing program already used by Metabolife, to ensure that ephedra products contain what they claim to contain.
- Strict labeling statements - Including a strict warning statement providing that individuals with pre-existing medical conditions should consult a physician or licensed qualified health care practitioner prior to product use.
- Strict science-based serving limits – Metabolife's proposal requires serving limits (up to 25 mg/serving and up to 100 mg/day) that are consistent with the results of a number of studies, including the Harvard/Columbia trial. There is an emerging science-based consensus that these limits are safe among an increasing number of states (including Hawaii, Michigan, Nebraska, Ohio, and Washington). These states have already adopted ephedra legislation or regulations that incorporate these limits.
- Mandatory manufacturer reporting to the FDA – Metabolife supports mandatory industry-wide reporting to the FDA.
- Full disclosure on product label – Labels on food and dietary supplements containing ephedra should be required to disclose: (1) the amount of ephedra in each serving (and the amount of product that constitutes a serving), (2) that taking more of the product than recommended (or taking it at greater frequencies) may increase the risk of negative health experiences, and (3) that the maximum recommended daily dose of ephedra is 100 mg.
- Consumer-Friendly Reporting – Metabolife's proposal would require labels on food and dietary supplements containing ephedra to list a toll free number for consumer inquiries that is maintained by the manufacturer, distributor, retailer, or third-party.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 15 2003

The Honorable Richard J. Durbin
Subcommittee on Oversight of Government Management,
Restructuring and the District of Columbia
Committee on Governmental Affairs
United States Senate
Washington, D.C. 20510-6260

Dear Senator Durbin:

Thank you for the letter of October 29, 2002, addressed to Dr. Lester M. Crawford, that included follow-up questions from the October 8, 2002 hearing on "Ephedra: Who is Protecting American Consumers?" Your questions appear in bold type followed by the Food and Drug Administration's (FDA or the Agency) responses.

1. **The AMA, Public Citizen and other concerned citizens have called on you to use your authority under the Dietary Supplement Health and Education Act (DSHEA) to remove ephedra-containing dietary supplements from the market. DSHEA gives the Secretary authority to remove such products if they "present a significant or unreasonable risk of illness or injury" or they "pose an imminent hazard to public health or safety." To date, over 16,000 adverse event reports have been submitted to the FDA related to ephedra-containing products. In the NEJM study mentioned above, 62 percent of the adverse events reported between June 1, 1997 and March 31, 1999 were judged to be definitely, probably, or possibly related to ephedra use. Would the Secretary agree that this clearly indicates that ephedra products are in fact an imminent hazard to certain consumers and they pose an unreasonable risk of illness or injury to many consumers?**

   FDA Response:

   The primary purpose of a voluntary adverse event reporting system is to generate signals of potentially related events, rather than assessing product safety. While a signal has been generated by the adverse event reports regarding ephedrine alkaloids, FDA has determined that questions remain on the likelihood and strength of association between ephedrine alkaloids and the adverse events reported to FDA. We are including all relevant information, including the *New England Journal of Medicine* (*NEJM*) study and an analysis of the adverse event reports, submitted to FDA by Metabolife, as a part of the evidence-based review that the RAND Corporation is doing. We are committed to evaluating all relevant information before choosing what course of action to pursue.

[Note: No Question 2 was submitted for response.]

3. **The FDA has taken steps to remove Phenylpropanolamine (PPA) from over-the-counter (OTC) drugs due to an increased risk of hemorrhagic strokes. Given the close similarity between PPA and ephedra and the fact that ephedra metabolizes in the body to yield a certain amount of PPA, would the Secretary agree that ephedra is likely to pose a similar threat to consumers? If the Secretary does not agree that ephedra is likely to pose a similar threat to consumers, please identify the scientific studies that the Secretary relies on to suggest that ephedra is safer than PPA.**

   FDA Response:

   Synthetic phenylpropanolamine (PPA) is commonly used in OTC drugs, such as cough or cold remedies and in appetite suppressants. Case reports linked the use of products containing PPA to hemorrhagic stroke. Based upon these reports, a case-control study was undertaken to study this association (see *NEJM*, 343/25: 1826-32; December 21, 2000: Kernan, et al., "Phenylpropanolamine and the Risk of Hemorrhagic Stroke"). FDA found the results of the case control study provided sufficient evidence to connect synthetic PPA in OTC drugs to increased risk of hemorrhagic stroke. FDA took action based on a connection established by the case control study.

   At this time, there is no specific scientific evidence to suggest that herbal ephedra is less or more safe than PPA. However, the safety of herbal ephedra is one of the issues being studied as part of the RAND Corporation science-based review and evaluation.

4. **Since 1983, the Food and Drug Administration has prohibited the marketing of OTC drugs containing combinations of caffeine with stimulants such as ephedrine or PPA because of the potential for misuse. No such restrictions exist for dietary supplement products. In the 1997 ephedra rule proposed by FDA, a provision was included that would prohibit the combination of other stimulant ingredients such as sources of caffeine with ephedrine alkaloids because the combination increases the stimulant effects of ephedrine alkaloids and the chance of consumer injury. When the Agency withdrew the 1997 proposed rule, it left this provision open for consideration. Does the Agency intend to finalize this portion of the rule?**

   FDA Response:

   After FDA's scientific experts have a chance to review RAND's conclusions, we will have additional information to assist the Agency in determining whether or not to finalize the proposed restriction on combining stimulants with ephedrine alkaloids in dietary supplements.

5. **In your September 19, 2002 response to my recent letters on ephedra, you mentioned that FDA has warned that people with certain conditions should consult a health**

care provider prior to using such products. What percentage of the general population do you believe is aware of such FDA warnings? Do you believe that such warnings are adequate to safeguard the public from harm?

FDA Response:

Your letter appears to refer to a June 14, 2002, Department of Health and Human Services press release that advised consumers with certain health conditions to consult a health care provider before taking any dietary supplement containing ephedrine alkaloids. It is very difficult to accurately assess what percentage of the U.S. population is aware of that press release and previous FDA warnings about ephedra products. Therefore, we cannot provide the estimate you request. The RAND report will help FDA scientists evaluate and develop future regulatory actions on dietary supplements containing ephedrine alkaloids. Potential future regulatory actions could include mandatory warning labels.

6. **Your recent letter also mentions that you have urged manufacturers to include FDA's 1-800-MEDWATCH telephone number on their product labels. Does the Administration support a mandatory requirement that such information be provided to consumers?**

FDA Response:

FDA is carefully considering this issue, but has not developed a final position at this time.

7. **The current regulatory scheme for dietary supplements involves voluntary reporting by manufacturers of adverse event reports. It is evident that most companies do not provide FDA with their reports. FDA has generally encountered resistance from companies when the Agency has requested AERs. The Agency, therefore, relies on reports by the general public even though many manufacturers do not even inform their consumers of the existence of the MEDWATCH system. Would the Administration support legislation to require mandatory reporting of adverse events either for dietary supplement manufacturers generally or specifically for the manufacturers of ephedra-containing dietary supplements?**

FDA Response:

FDA has not developed a legislative position on mandatory Adverse Event Reports (AERs) by supplement manufacturers. FDA has encouraged supplement manufacturers to voluntarily provide AERs to the Agency. Recently, FDA began sending the suppliers or manufacturers adverse event notification letters to inform them that FDA is aware of an adverse event associated with one of their products.

8. **Metabolife has recently provided the FDA with 14,700 adverse event reports. However, these reports are all redacted. Has this redaction impeded the FDA's**

ability to follow up on these AERs with victims and their family members? How does FDA propose to investigate these AERs without contact information? Has the agency followed up with Metabolife to ask for contact information for certain AERs?

FDA Response:

We asked Metabolife for the unredacted adverse event reports and they have declined to provide them, citing State privacy laws. Currently, we are in the process of evaluating the adverse events provided by Metabolife in order to determine whether the redactions are likely to affect our ability to review the reports.

9. **Some companies do provide FDA with complete AERs on a voluntary basis. Please outline the confidentiality protections the FDA provides for these records. Additionally, please outline the provisions in the Federal medical privacy regulations that deal with adverse event reporting.**

FDA Response:

All AERs that are received by FDA are subject to redaction to protect confidentiality, consistent with the Freedom of Information Act and its exemptions. In handling and investigating AERs, FDA takes great care to protect confidential commercial information and information that would jeopardize personal privacy.

The Federal Health Insurance Portability and Accountability Act (HIPAA) of 1996 mandated new security standards to protect an individual's health information, while permitting the appropriate access and use of that information by health care providers, clearinghouses, and health plans. HIPAA regulations bind "covered entities." Covered entities are health plans, health care clearinghouses, and health care providers who conduct certain health care transactions electronically. FDA is not a covered entity and, therefore, the HIPAA regulations do not directly apply to FDA.

However, the HIPAA regulations apply to covered entities that want to share adverse event information with a company responsible for an FDA-regulated product. Under the HIPAA regulations (Title 45, Code of Federal Regulations §164.512(b)(1)(iii)), a covered entity may disclose protected health information about a person who experienced an adverse event to a person subject to the jurisdiction of FDA, who has responsibility for the FDA-regulated product or activity, without receiving authorization from the person who experienced the adverse event. The covered entity's disclosure, to the person subject to the jurisdiction of FDA, is subject to the HIPAA regulations' "minimum necessary standard." This initial disclosure allows companies responsible for FDA-regulated products to obtain adequate adverse event reports. These adverse event reports may (or must, depending on the situation) be submitted to FDA by the company responsible for the FDA-regulated product. After FDA receives the adverse event reports, the AERs are redacted before public disclosure to protect confidentiality consistent with the Freedom of Information Act (FOIA) and the Privacy Act. In handling and investigating AERs, FDA takes great

care to protect confidential commercial information and information that would jeopardize personal privacy. Under the FOIA and the Privacy Act, FDA's treatment of personal privacy information is the same regardless of whether the company submitted the adverse event report voluntarily or was required to submit the report to FDA.

10. **You mention in your recent letter that HHS has commissioned a study by the RAND Corporation to review the current scientific literature on the safety and efficacy of dietary supplements containing ephedrine alkaloids. Please discuss the relevance of these studies given the fact that most published clinical studies included pre-screening of participants and exclusion of those with preexisting conditions. The methodologies used in these studies bear little relevance to the patterns of consumption by the general public, where consumption takes place without a prescription, without prior evaluation of the health conditions that may suggest that a consumer is a poor candidate for consumption of this product, and without medical supervision while consuming the product. In one study by Boozer et al., 11 percent of the potential participants were not included because of prescreening and a further 48 percent dropped out for a multiplicity of reasons, including health conditions that led to their being judged unsuitable for participation. Please comment on what knowledge would actually be gained by analysis of such studies.**

FDA Response:

It is FDA's understanding that all available studies, regardless of subject participation criteria or methodology, are a part of the evidence-based review by RAND. Both FDA and RAND, in the course of the reviews of all available information, will evaluate the relevance and quality of each study, including the methodology, patient selection, etc. These reviews will also study how products are labeled and used in the marketplace as compared to how they were used in the clinical studies.

11. **In an article in Mayo Clinic Proceedings this past January, researchers reviewed the cases of 37 patients who suffered adverse cardiovascular events specifically sudden death, myocardial infarction, or stroke and found that "the cardiovascular toxic effects of ephedra were not limited to massive doses." Of the 37 patients in the study who experienced one of the aforementioned health problems, 36 were using amounts no larger than the manufacturer recommended. Does the Secretary agree that this study suggests that there is no safe dose of ephedra?**

FDA Response:

FDA has not made a determination based on that or any other individual study. Rather, FDA has requested that RAND conduct a comprehensive review of available scientific information regarding ephedra, in order to more fully evaluate its safety. Thank you for your inquiry. If you have any further questions or concerns, please let me know.

Sincerely,

Amit K. Sachdev
Associate Commissioner
for Legislation

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November 1, 2002

VIA FASCIMILE (202) 228-0400

Hon. Richard J. Durbin
United States Senate
332 Dirksen Senate Office Building
Washington, DC 20510

Dear Senator Durbin:

As a follow up to our letter dated October 21, 2002, that was written on behalf of our client, NVE Pharmaceuticals ("NVE"), of Newton, New Jersey, we wanted to supplement our responses to question numbers 8 and 11 of your September 27, 2002 letter, specifically regarding your belief that ephedra is addictive and the demographics of NVE's customers, respectively. We stress the importance of reviewing all of the scientific information regarding ephedra, examples of which are provided herein, prior to coming to any conclusion regarding its safety or whether or not it is addictive.

8. NVE repeats that it is unaware of any scientific evidence in existence that supports the conclusion that ephedra products are addictive. Indeed authoritative texts actually take the contrary position, that ephedrine is not addictive. Examples of such texts are as follows:

- In *Goodman and Gilman's The Pharmacological Basis of Therapeutic,* AG Gilman, LS Goodman et al, editors (7th ed., New York, MacMillan Publishing Co. 1985) when discussing ephedrine's toxicity and side effects, no mention of addiction or dependence is made. Dependence is discussed, however, in the section of the text on amphetamines. The amphetamine section also makes reference to a separate chapter discussing drug addiction and abuse; and this chapter does not mention ephedrine in its list of CNS sympathomimetics and other agents that produce subjective effects that resemble those of amphetamine.

- In *Martindale: The Extra Pharmacopoeia,* JEF Reynolds, editor (London: The Pharmaceutical Press, 1989) the listing for ephedrine provides few specific precautions, none of which are dependence. The book refers to the overall discussion of sympathomimetics (of which ephedrine is included) for precautions relevant to the class, none of which include a concern related to dependence or addiction.

With regard to the safety of dietary supplements containing the combination of ephedra extract containing ephedrine alkaloids and caffeine, studies have been conducted to test these products' long-term safety and efficacy for weight loss. One such study, *Herbal ephedra /caffeine for weight loss: a 6-month randomized safety and efficacy trial*, was recently published in the International Journal of Obesity and concluded that the supplement reduced body weight and fat and improved blood lipids without significant adverse events. A copy of this 6-month randomized, double-blind placebo controlled trial is attached hereto for your review.

11. Additionally, NVE supplements its response to question number 11 of your September 27, 2002 letter by submitting that the majority of its customers are between the ages 18 to 49 years of age and are both male and female.

If additional information becomes available to us that we believe will be of some assistance to you and the Subcommittee, we will promptly forward it to you.

Yours truly,

ULLMAN, SHAPIRO & ULLMAN, LLP

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Enclosure

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PAPER

Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial

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OBJECTIVE: To examine long-term safety and efficacy for weight loss of an herbal Ma Huang and Kola nut supplement (90/192 mg/day ephedrine alkaloids/caffeine).
DESIGN: Six-month randomized, double-blind placebo controlled trial.
SUBJECTS: A total of 167 subjects (body mass index (BMI) 31.8 ± 4.1 kg/m²) randomized to placebo ($n = 84$) or herbal treatment ($n = 83$) at two outpatient weight control research units.
MEASUREMENTS: Primary outcome measurements were changes in blood pressure, heart function and body weight. Secondary variables included body composition and metabolic changes.
RESULTS: By last observation carried forward analysis, herbal *vs* placebo treatment decreased body weight (-5.3 ± 5.0 *vs* -2.6 ± 3.2 kg, $P < 0.001$), body fat (-4.3 ± 3.3 *vs* -2.7 ± 2.8 kg, $P = 0.020$) and LDL-cholesterol (-8 ± 20 *vs* 0 ± 17 mg/dl, $P = 0.013$), and increased HDL-cholesterol ($+2.7 \pm 5.7$ *vs* -0.3 ± 6.7 mg/dl, $P = 0.004$). Herbal treatment produced small changes in blood pressure variables ($+3$ to -5 mmHg, $P \leq 0.05$), and increased heart rate (4 ± 9 *vs* -3 ± 9 bpm, $P < 0.001$), but cardiac arrhythmias were not increased ($P > 0.05$). By self-report, dry mouth ($P < 0.01$), heartburn ($P < 0.05$), and insomnia ($P < 0.01$) were increased and diarrhea decreased ($P < 0.05$). Irritability, nausea, chest pain and palpitations did not differ, nor did numbers of subjects who withdrew.
CONCLUSION: In this 6-month placebo-controlled trial, herbal ephedra/caffeine (90/192 mg/day) promoted body weight and body fat reduction and improved blood lipids without significant adverse events.
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Keywords: Ma Huang; Kola nut; ephedrine; ephedra alkaloids; obesity; weight loss; clinical trial; herbal medicine; alternative medicine

Introduction

Since passage of the Dietary Supplement Health and Education Act (DSHEA) by Congress in 1994, classifying herbal compounds as 'dietary supplements', marketing of such products in the USA has escalated. Sales are estimated to have risen from $9.8 billion in 1995 to $14.7 billion in 1999.[1] A large portion of that market is devoted to herbal dietary supplements containing ephedra, with three billion servings reportedly sold[2] and approximately 12 million individuals estimated to be using such products in 1999.[2] While the consequence of DSHEA is that the Food and Drug Administration (FDA) does not regulate the sales of these products, the FDA does collect anecdotal reports of adverse events and these reports have raised concerns about the safety of ephedra products by the FDA[3] and the media.[2,4,5]

A major reason for use of ephedra-containing herbal products is body weight reduction. Questions of safety and efficacy are central issues for any agent used for human weight control. Ephedrine, the primary active ingredient of herbal ephedra, has been well studied both alone, and in combination with caffeine. Placebo-controlled studies have demonstrated that ephedrine, particularly in combination

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with caffeine, is effective in promoting weight loss without increasing serious adverse events[6–9] and the combination is used for that purpose in Europe.[10] Despite this literature for synthetic ephedrine, the lack of data demonstrating similar effects for herbal ephedra has contributed to questions of both its safety and efficacy.[2]

Two clinical trials demonstrating efficacy of herbal ephedra combinations for reduction of body weight and fat have been completed.[11,12] Both studies, however, were only 8 weeks in duration, thus limiting conclusions about longer-term safety. The purpose of the present 6 month study was to provide objective assessment of safety and efficacy for weight-loss of a herbal dietary supplement containing Ma Huang herbal ephedra and Kola nut (as sources of ephedrine alkaloids and caffeine). While the emphasis of the present investigation was on the detailed monitoring of blood pressure, heart rate and disrhythmias during the acute phase of treatment, this study is also the first reported long-term, clinical trial of a herbal preparation containing ephedrine alkaloids and caffeine in combination.

Methods

Study design

The study was a prospective, two-arm, 6-month, randomized, double-blind, placebo-controlled, clinical safety and efficacy trial conducted at two sites (New York and Boston). Efficacy was assessed by measuring changes in body weight, body fat and waist and hip circumferences. Safety was assessed by determining changes in cardiovascular parameters, blood chemistries, liver enzymes, self-reported symptoms and reasons for withdrawal from the study.

Randomization of equal numbers of subjects to placebo or herbal groups was achieved using a random number table, with block sizes varying between two and eight. A statistician not involved in the study produced separate randomization codes for the two sites. Sealed copies of these codes were provided to the investigators for emergency identification. Otherwise, codes remained sealed until completion of the study, when another statistician, who was not involved in carrying out the study, was provided with the code and the data for analysis.

Statistical analyses were designed on an 'intention-to-treat' basis to achieve a statistical power of 0.90 and a 0.05 type I error for a two-sided test. Power calculations were primarily concerned with the possibility of adverse effects during the acute phase of the study (weeks 1–4). Using a two-sample t-test, a minimum of 66 subjects in each group would have been sufficient to detect a difference of 4.1 mmHg systolic blood pressure (s.d. = 7.23), a difference of 4.6 mmHg diastolic blood pressure (s.d. = 6.0), and also a difference in heart rate of 6 bpm (s.d. = 10.36). The study was approved by the Institutional Review Boards of St Luke's-Roosevelt Hospital Center in New York and Beth Israel Deaconess Medical Center in Boston and all subjects gave written consent prior to participation.

Subjects

Subjects, recruited by advertisements in local newspapers and flyers, were interviewed by telephone. Eligibility requirements included age between 18 and 80 y and body mass index (BMI) ≥ 25 and $\leq 40\,kg/m^2$. Subjects were recruited without regard to racial or ethnic background. Smokers were not excluded, nor were diabetics with reasonable control (hemoglobin A1C $\leq 7.8\%$) who did not take insulin or oral diabetic medication. Subjects were excluded if they were not otherwise healthy, were pregnant or nursing, had recently lost weight or participated in other diet or drug studies, or if they reported consumption of $> 500\,mg$/day caffeine (see Appendix I for complete list of exclusions).

For inclusion in the study, subjects were required to successfully pass a medical screening by a study physician. This included medical history and symptom evaluations, a physical examination that included measurement of height and weight, sitting blood pressure and pulse rate, an EKG and a laboratory evaluation including blood test and urine toxicology screen. Subjects were not included if blood pressure was $\geq 140/90$ or if values from laboratory tests were outside normal ranges. Screening also included 24 h measurement of blood pressure by ambulatory blood pressure monitor (ABPM) and heart rhythm by Holter monitor. Subjects were excluded if monitoring detected hypertension (defined as mean 24 h systolic BP $\geq 139\,mmHg$ or mean 24 h diastolic BP $\geq 87\,mmHg$) or significant ventricular ectopy (including > 1000 premature beats/24 h, 'R on T' phenomenon, torsades de pointes, or QT interval prolongation; runs of supraventricular tachycardia > 1 min, or new onset atrial fibrillation; or presence of any other clinically significant rhythm disturbance). Holter data and EKGs of subjects with multiform or multifocal ventricular events (MFVE) were reviewed by the study cardiologist prior to admission. Those without evidence of other significant cardiac disease were allowed to enroll in the study.

Following successful medical screening, subjects returned within 1–4 weeks for a baseline evaluation that included repeat measurements of height, weight, sitting blood pressure and heart rate as well as measurement of waist and hip circumferences and body fat. The symptom questionnaire was again completed and ABPM and Holter monitors worn for a second 24 h period. Subjects who did not fall into any of the exclusion categories after these baseline measures were randomized to either placebo or the herbal preparation (Ma Huang/Kola nut).

Treatment

At randomization, subjects were counseled to eat normally, but limit intake of dietary fat to 30% of calories and to exercise moderately (eg walking 30 min/day, three times a week). Handouts on good eating habits and a progressive walking/exercise program were provided. Active and placebo tablets were supplied in opaque white plastic bottles containing a known number of tablets. Subjects were directed to take

two tablets, 30 min before each meal, three times a day (six tablets per day, the maximum amount recommended on most ephedra-containing commercial products) and to return unused pills, which were counted to determine adherence.

The active preparation was a herbal mixture (provided by Science, Toxicology and Technology, San Francisco, CA, USA) containing Ma Huang (NutraTech Inc, Gardena, CA, USA) and Kola nut (Ashland Distribution Corp, Santa Anna, CA, USA) as the only active ingredients. Each tablet was specified to contain 15 mg of total ephedrine alkaloids and 32 mg of caffeine per tablet, for a total daily amount of ephedrine alkaloids and caffeine of 90 and 192 mg, respectively. The placebo was an identical appearing tablet containing inert ingredients. Certificates of analyses for ephedrine alkaloid and caffeine content provided to the supplier were validated by the investigators.

During the initial month of treatment, subjects returned weekly to pick up pills, review dietary and exercise advice, complete the symptom questionnaires and have weight, sitting blood pressure and pulse rate measured. At weeks 1, 2 and 4, ABPM and Holter monitors were worn for additional 24 h periods. At the end of the first month, another blood sample was taken for assessment of ALT, creatinine and HCG (in women of child-bearing age).

During the subsequent 20 weeks, subjects returned every 4 weeks for a 30 min visit. The symptom questionnaire was completed, and a brief dietary and symptom review and physical evaluation by the study coordinator including weight, sitting blood pressure and heart rate was taken. Blood was taken for ALT, creatinine and HCG (in women of child-bearing age) at each of these visits.

At week 12 and 24 (final) visits, additional fasting blood samples were taken, EKGs recorded, and measurements of waist and hip circumferences and body fat content repeated.

Measurements

Medical and nutrition history and self-reported symptoms were evaluated by questionnaires designed by the investigators (PAD & TM) for this study. Height was measured to the nearest 0.5 cm by stadiometer (Holtain, Crosswell, Wales, UK). Body weight was measured to the nearest 0.1 kg using a digital scale (NY site: Weight Tronix, New York, USA; Boston site: Detecto-Medic, Detecto Scales Inc, Brooklyn, NY, USA). Trained personnel measured waist and hip circumferences at standard anatomical locations.[13] Total body fat was assessed by bioimpedance (Tanita Inc: TBF 310, Arlington Heights, IL, USA). Siri's two-compartment model was used to convert measured body density to fat.[14]

Blood studies included serum glucose and lipids (cholesterol and triglycerides), liver and renal function tests (creatinine, ALT and AST), TSH, standard electrolytes, a complete blood count (NY site: Quest Diagnostic Laboratory, Teterboro, NJ, USA; Boston site: Veterans Admistration North Texas Health Care System, Dallas, TX, USA). Toxicologic urine screens (see Appendix II for list of tests) were performed by Diagnostic Laboratories, Vanderbilt University Medical Center, Nashville, TN, USA.

Data from Holter and ABPM monitors were analyzed by Space Laboratories (Seattle, OR, USA), with follow-up evaluations as required by the study cardiologist. EKGs of the NY subjects were evaluated for four intervals (RRR, P-R, QT_c, QRS), QRS amplitude and cardiac rhythm.

Three independent laboratories (Alpha Chemical and Biomedical Laboratories, Petaluma, CA, USA; Industrial Laboratories Company Inc, Denver, CO, USA; and San Rafael Chemical Services, Salt Lake City, UT, USA) analyzed samples of active and placebo tablets by high pressure liquid chromatography (HPLC) for ephedrine, total ephedrine alkaloids and caffeine.

Statistical methods

Values are presented in the text and tables as mean ± standard deviation (s.d.) and in the figures as means ± standard errors (s.e.). The tables show statistical comparisons between the groups by the 'last observation carried forward' (LOCF) method for dealing with missing data. Values for subjects who dropped out after the acute phase (week 4) were carried forward to each subsequent time point in the trial. Figures present analyses of only data that was actually available for subjects at each time point, with no values carried forward for subjects who dropped out.

Effect of treatment on weight, body fat, waist and hip circumferences, sitting blood pressure, heart rate and blood chemistries were assessed by using a repeated measures ANOVA test for group by time interaction, followed by pair-wise *t*-tests. Repeated categorical data (eg cardiac arrhythmias) were analyzed using a weighted least squares model (WLS)[15] followed by pair-wise chi-square tests, where possible. Reasons for withdrawal in each group were compared using chi-square tests. All analyses were conducted using a two-tailed 0.05 alpha level.

Results

Subject disposition

Of 284 subjects who appeared eligible by telephone screen, 167 were randomized (83 to ephedra/caffeine and 84 to placebo; Figure 1). Of those not randomized, most either chose not to participate (45) or were ineligible due to violations of protocol inclusion requirements (15) or non-compliance with protocol requirements (8). Thirty-one were ineligible for medical reasons that were exclusionary for the protocol.

During the first 4 weeks of the study, the acute phase, 17 (20%) randomized subjects withdrew from each group, with 66 remaining in the herbal group and 67 remaining in the placebo group. During the remaining 5 months of the study, there were 20 (24%) withdrawals from the herbal group and 26 (31%) from the placebo group.

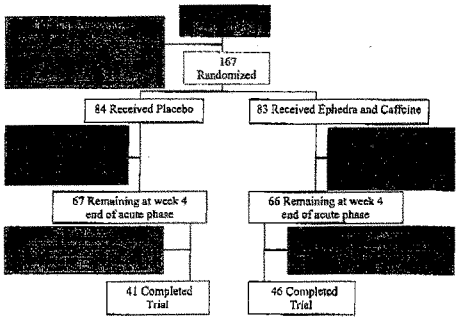

Figure 1 Disposition of all subjects recruited for the study.

Baseline physical characteristics of subjects

Subjects in the two treatment groups (P, placebo: H, herbal) did not differ ($P > 0.05$) initially in age (46.0±12.2 (mean±s.d.); 44.5±12.4 y), body weight (88.1±14.8; 87.9±13.9 kg), or BMI (31.7±4.0; 31.8±4.4 kg/m^2; Table 1). Distributions of gender and self-identified race were also not significantly different between groups (P, 86% female; H, 78% female; (P, 70% Caucasian, 15% African-American and 7% Hispanic; H, 69% Caucasian, 11% African-American and 12% Hispanic).

Herbal analysis

Independent laboratory HPLC analysis detected, per placebo tablet, less than 0.3 mg (range, non-detectable to <0.3 mg) each of caffeine and total ephedrine alkaloids and, per herbal tablet, 32.7±1.5 mg caffeine and 14.4±1.6 mg total ephedrine alkaloids.

Table 1 Baseline characteristics of all randomized subjects

Characteristic	*Placebo (n = 84)*	*Herbal (n = 83)*
Gender		
Men (n (%))	12 (14%)	18 (22%)
Women (n (%))	72 (86%)	65 (78%)
Race (n (%))		
Caucasian	59 (70%)	57 (69%)
African-American	13 (15%)	9 (11%)
Hispanic	6 (7%)	10 (12%)
Indian, Asian, Other	5 (6%)	6 (7%)
	X±s.d.	X±s.d.
Age (y)	46.0±12.2	44.5±12.4
Weight (kg)	88.1±14.8	87.9±13.8
Body mass index (kg/m^2)	31.7±4.0	31.8±4.4

Race was by self-identification. One subject in each group did not identify race.

Adherence

Adherence, calculated as the percentage of pills not returned by the subject relative to the number of pills supplied, did not differ between groups (P, 90±11%; H, 89±10%).

Treatment effects

Body weight and body composition. Results of LOCF analyses of physical values are shown in Table 2. Both treatment groups lost significant ($P < 0.001$) amounts of body weight and body fat over the 6 months of the study. Losses in the herbal group, however, were greater than in the placebo for both body weight (H, −5.3±5.0; P, −2.6±3.2 kg; $P < 0.001$) and body fat (H, −4.3±3.3 kg, P, −2.7±2.8 kg, $P = 0.020$).

Both groups also had significant decreases in waist (P, −2±6 cm, $P = 0.004$ and H, −6±5 cm, $P < 0.001$) and hip circumferences (P, −4±4 cm, $P < 0.001$ and H, −6±5, $P < 0.001$), but again these changes were significantly greater in the herbal *vs* the placebo group for both waist ($P = 0.005$) and hip circumferences ($P = 0.018$). There were no significant interactions or differences between the treatment groups in waist–hip ratio (not shown).

Mean values for all subjects for whom data were collected at each time point are shown for body weight in Figure 2 and for body fat in Figure 3. Of subjects who completed the 6-month study, those in the herbal group lost significantly more body weight than those in the placebo group (P, −3.1±4.0; H, −7.0±4.3 kg; $P < 0.001$). Body fat was also significantly decreased by herbal treatment for subjects with

Table 2 LOCF analysis of physical values[a]

Measure	Study period	Group: Placebo X±s.d. (P-value)[b]	Group: Herbal X±s.d. (P-value)[b]	P[c]
Body weight (kg)	Baseline	87.9±13.9	88.1±14.8	0.955
	6 month	85.3±14.7	82.8±15.4	0.319
	Change	−2.6±3.2 (<0.001)	−5.3±5.0 (<0.001)	<0.001
	ANOVA	Time×group interaction: P<0.001		
Body fat mass (kg)	Baseline	34.2±9.9	32.6±9.1	0.451
	6 month	31.5±10.6	28.2±9.2	0.150
	Change	−2.7±2.8 (<0.001)	−4.3±3.3 (<0.001)	0.020
	ANOVA	Time×group interaction: P<0.020		
Waist circumference (cm)	Baseline	98±12	97±13	0.699
	6 month	96±13	92±13	0.135
	Change	−2±6 (0.004)	−6±5 (<0.001)	0.005
	ANOVA	Time×group effect: P=0.004		
Hip circumference (cm)	Baseline	117±10	115±9	0.270
	6 month	113±10	109±10	0.033
	Change	−4±4 (<0.001)	−5±5 (<0.001)	0.018
	ANOVA	Time×group effect: P=0.044		
Systolic blood pressure (mmHg)	Baseline	120±11	119±11	0.877
	6 month	120±12	118±12	0.405
	Change	0±11 (0.659)	−1±9 (0.289)	0.313
	ANOVA	Time×group interaction: P=0.177		
Diastolic blood pressure (mmHg)	Baseline	79±8	77±8	0.365
	6 month	79±9	78±9	0.397
	Change	0±8 (0.729)	<1±8 (0.836)	0.928
	ANOVA	Time×group interaction: P=0.128		
Heart rate (bpm)	Baseline	74±7	69±8	0.001
	6 month	71±9	73±10	0.130
	Change	−3±9 (0.008)	4±9 (0.001)	<0.001
	ANOVA	Time×group interaction: P<0.001		

[a]Treatment was a herbal supplement containing 90 mg ephedra and 192 mg caffeine/day ($n=69$/group for weight, SBP, DBP, heart rate; $n=38$ for placebo and 39 for herbal for body fat; $n=48$ for placebo and 47 for herbal for waist and hip).
[b]P-value for within-group change from baseline compared by paired samples t-test.
[c]Treatment vs placebo groups were compared by ANOVA test for group×time interaction followed by pair-wise t-tests of baseline and 6 month values and change from baseline at 6 months, with alpha set at 0.05.

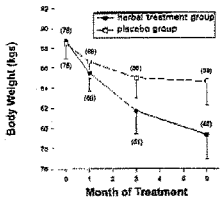

Figure 2 Effect of herbal and placebo treatment on change in body weight. Values shown include all subjects in herbal and placebo treatment groups for whom there was data at each time point (n).

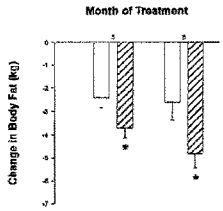

Figure 3 Change in body fat from baseline after 3 months and 6 months of herbal or placebo treatment. Open bars represent placebo ($n=38$ at 3 months, $n=25$ at 6 months). Hatched bars represent herbal treatment ($n=39$ at 3 months, $n=26$ at 6 months). *$P\leq 0.05$.

complete body composition data at 3 months (P, −2.4±2.6 kg; H, −3.7±2.6 kg, $P=0.031$) and 6 months (P, −2.6±3.9 kg; H, −4.8±3.2 kg, $P=0.032$).

Blood pressure and heart rate at office visits. Mean systolic and diastolic blood pressure measurements did not differ between treatment groups at any time point, nor was there a significant group-by-time interaction for either variable, whether analyzed by LOCF (Table 2) or using all available data (not shown). Change in heart rate was significantly different ($P<0.001$) between groups (P, −3±9, $P=0.008$; H, 4±9, $P<0.001$). Time-by-group interaction was also significant ($P<0.001$), with values in the herbal group compared with placebo that were lower at baseline (by 4±3.9 bpm, $P=0.001$), but not significantly different (4 bpm±3.9, $P=0.130$) at 6 months (Table 2, LOCF). Analysis of all available data for heart rate showed similar results to LOCF analysis, with a significant time-by-group interaction ($P<0.001$), and differences between groups that were significant only at baseline (when H was lower than P, $P<0.01$) and at 3 months (when H was higher than P, $P<0.05$; not shown).

Treatment groups did not differ in EKG data, analyzed at the NY site, for any of the four intervals evaluated (RR, P-R, QTc, QRS) or for QRS amplitude and heart rhythm (not shown).

Blood pressure by 24 h monitor. Data from 24 h monitors at baseline, and weeks 1, 2 and 4 were compared for 24 h mean, daytime mean (6:00 am to midnight) and night-time mean (midnight to 6:00 am), for SBP, DBP, minimum SBP and DBP, maximum SBP and DBP and mean arterial pressure (Table 3).

Effects of herbal treatment on blood pressure were small, but time-by-group interactions were statistically significant ($P\leq0.05$) for: 24 h averages of SBP, DBP and minimum SBP; and for daytime averages of SBP and minimum SBP. Maximum increases over baseline at 4 weeks in the herbal group

Table 3 Twenty-four-hour ambulatory blood pressure monitor data

		24 h average			Day (6:00 am–midnight)			Night (midnight–6:00 am)		
		Placebo	Herbal	P	Placebo	Herbal	P	Placebo	Herbal	P
SBP (mmHg)	B	118±8	120±8	0.403	120±8	121±8	0.602	108±8	110±9	0.179
	W1	118±8	118±8	0.754	120±9	119±10	0.462	106±10	110±11	0.230
	W2	116±8	118±8	0.133	118±8	120±8	0.251	106±9	111±10	0.005
	W4	116±11	120±9	0.020	118±11	121±8	0.060	107±10	111±10	0.014
	ANOVA	Time×group interaction: $P=0.016$			Time×group interaction: $P=0.021$			Time×group interaction: $P=0.152$		
DBP (mmHg)	B	72±7	72±6	0.887	74±7	73±6	0.252	63±6	63±7	0.991
	W1	72±10	72±7	0.637	74±7	73±6	0.340	64±8	65±8	0.646
	W2	71±10	73±7	0.200	74±7	74±6	0.895	63±7	64±9	0.193
	W4	71±11	75±8	0.056	74±8	76±11	0.251	61±10	65±10	0.015
	ANOVA	Time×group interaction: $P=0.020$			Time×group interaction: $P=0.053$			Time×group interaction: $P=0.066$		
MINSBP (mmHg)	B	95±7	95±8	0.766	98±8	98±8	0.454	98±8	99±10	0.277
	W1	94±9	95±10	0.729	98±11	98±11	0.991	97±10	100±11	0.160
	W2	91±9	95±9	0.030	95±11	99±10	0.035	94±10	99±10	0.004
	W4	93±10	97±10	0.012	96±12	101±10	0.021	96±10	100±11	0.043
	ANOVA	Time×group interaction: $P=0.008$			Time×group interaction: $P=0.017$			Time×group interaction: $P=0.257$		
MINDBP (mmHg)	B	50±6	49±8	0.400	53±7	53±8	0.798	52±7	54±8	0.263
	W1	52±7	49±9	0.116	54±7	54±10	0.819	54±8	55±8	0.695
	W2	51±6	50±10	0.606	54±7	54±8	0.917	52±7	52±9	0.884
	W4	50±7	51±9	0.576	54±8	55±8	0.652	52±7	54±9	0.323
	ANOVA	Time×group interaction: $P=0.089$			Time×group interaction: $P=0.868$			Time×group interaction: $P=0.652$		
MAXSBP (mmHg)	B	143±12	143±11	0.741	142±12	143±11	0.922	119±9	122±11	0.077
	W1	142±13	141±12	0.917	141±13	141±12	0.713	119±12	121±13	0.370
	W2	140±12	141±10	0.591	140±12	141±10	0.885	117±12	121±13	0.046
	W4	140±14	140±13	0.716	140±14	138±21	0.559	118±12	122±12	0.078
	ANOVA	Time×group interaction: $P=0.941$			Time×group interaction: $P=0.803$			Time×group interaction: $P=0.683$		
MAXDBP (mmHg)	B	93±8	93±10	0.969	93±9	93±9	0.991	72±8	73±10	0.859
	W1	94±11	92±8	0.104	94±12	92±7	0.156	75±10	74±7	0.339
	W2	92±8	92±10	0.885	92±8	91±8	0.388	73±9	73±8	0.991
	W4	94±12	93±8	0.576	94±12	92±8	0.295	73±10	76±10	0.044
	ANOVA	Time×group interaction: $P=0.433$			Time×group interaction: $P=0.605$			Time×group interaction: $P=0.059$		
MAP (mmHg)	B	87±6	87±6	0.877	90±6	90±6	0.537	79±6	79±7	0.649
	W1	86±7	86±6	0.452	90±8	89±8	0.697	80±8	80±7	0.987
	W2	85±7	85±6	0.920	89±7	89±5	0.981	78±8	80±7	0.134
	W4	85±8	86±7	0.473	89±9	90±6	0.494	78±8	80±8	0.076
	ANOVA	Time×group interaction: $P=0.271$			Time×group interaction: $P=0.452$			Time×group interaction: $P=0.175$		

SBP, systolic blood pressure; DBP, diastolic blood pressure; MINSBP, minimum systolic blood pressure; MINDBP, minimum diastolic blood pressure. MAXSBP, maximum systolic blood pressure; MAXDBP, maximum diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate. S, Screen (prior to treatment); B, baseline (prior to treatment); W1, W1, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n=67$) or placebo (P, $n=66$).

were 3 mmHg (day DBP, day min SBP, both $P=0.02$) and significant ($P \leq 0.05$) decreases occurred in max SBP for both 24 h and day averages (−3 and −5 mmHg). Most of the differences in change over time were due to decreases in the placebo group, with small or no change in the herbal group. There were no statistically significant time-by-group interactions for minimum DBP, for maximum SBP or DBP or for mean arterial pressure.

Holter monitor data. As shown by office visit measurements, there was a significant time-by-group interaction ($P=0.020$) for heart rate assessed by Holter monitor. Between-group differences were significant ($P<0.05$) only at baseline, when the heart rate of the herbal group was lower by 3 bpm (Table 4). Heart rate over the 4 weeks of Holter measurement increased by 1±14 bpm in the herbal group *vs* a decrease of 5±13 bpm in the placebo group ($P=0.026$).

None of the cardiac arrhythmias assessed were increased by herbal treatment. The only significant time-by-group interaction ($P<0.024$), for percentage of subjects displaying incidents of bradycardia (≤60 bpm) was due to a decrease in the herbal group (−12%, *vs* no change in the placebo group). Ventricular events/h did not differ between groups at any time point, nor did the percentage of subjects with tachycardia (≥100 bpm), MFVEs or runs of ventricular events.

Blood chemistries. By LOCF analysis, there were statistically significant 6-month improvements with herbal treatment in serum levels of total cholesterol (−6±23 mg/dl, $P=0.03$), LDL-cholesterol (−8±20 mg/dl), HDL-cholesterol (+3±6, $P=0.0001$), and triglycerides (−12±41 mg/dl, $P=0.01$), with no change in blood glucose (0±10 mg/dl, $P=0.68$; Table 5). These changes were significantly different from placebo, however, only for LDL-cholesterol, HDL-cholesterol and glucose. The difference in change in serum levels

Table 4 LOCF analysis of Holter monitor data

Measure	Study period	Group: Placebo	Group: Herbal	P
Pulse, average bpm/24 h ± s.d.	Baseline	78±8	75±11	0.050
	Week 1	74±10	77±12	0.169
	Week 2	74±10	77±12	0.211
	Week 4	73±12	76±14	0.370
	ANOVA	Time×group interaction: $P=0.020$		
Ventricular events/h, median (inter-quartile range)	Baseline	0.08 (0.57)	0.06 (0.14)	0.168
	Week 1	0.04 (0.29)	0.00 (0.13)	0.129
	Week 2	0.06 (0.44)	0.04 (0.29)	0.400
	Week 4	0.04 (0.36)	0.04 (0.16)	0.250
Ventricular couplets (%)	Baseline	3.08%	2.94%	1.0
	Week 1	3.08%	5.88%	0.68
	Week 2	3.08%	8.82%	0.27
	Week 4	13.85%	4.41%	0.07
	WLS	Time×group interaction: $P=0.061$		
Runs ventricular events (%)	Baseline	0.00%	2.26%	0.237
	Week 1	3.08%	0.00%	0.237
	Week 2	1.54%	2.94%	1.000
	Week 4	1.54%	0.00%	0.489
Multifocal ventricular events (%)	Baseline	33%	25%	0.288
	Week 1	27%	19%	0.263
	Week 2	27%	29%	0.784
	Week 4	35%	25%	0.213
	WLS	Time×group interaction: $P=0.369$		
Bradycardia (%)	Baseline	83%	92%	0.101
	Week 1	83%	72%	0.216
	Week 2	89%	78%	0.103
	Week 4	83%	80%	0.681
	WLS	Time×group interaction: $P=0.024$		
Tachycardia (%)	Baseline	97%	100%	0.151
	Week 1	100%	100%	
	Week 2	100%	98%	0.319
	Week 4	100%	100%	

Pulse analyzed by ANOVA followed by pair-wise t-tests of baseline and 6 month values and change from baseline at 6 months, with alpha set at 0.05.
Ventricular events reported as median (inter-quartile range); analyzed by Wilcoxon/Mann–Whitney non-parametric test.
Ventricular couplets, MFVEs, bradycardia and tachycardia reported as percentage of subjects, analyzed by WLS.
Runs of ventricular events and tachycardia reported as percentage (WLS not permitted because of 0 values).

of glucose was due to a significant increase in the placebo group (3±9 mg/dl, $P=0.02$).

As with the LOCF analyses, analysis of changes in serum levels of blood lipids and glucose of all subjects for whom there was complete data found significant differences for P *vs* H for LDL-cholesterol (−0.8±24.2 *vs* −12.9±23.1 mg/dl, $P=0.026$), HDL-cholesterol (−0.5±9.4 *vs* 4.4±6.6 mg/dl, $P=0.011$) and glucose (5.3±12.1 *vs* −0.8±12.8 mg/dl, $P=0.036$; data not shown). Differences between groups for changes in serum triglycerides and total cholesterol were not significantly different ($P>0.05$).

There were no significant changes or differences between the two groups at any time point for serum levels of any of the electrolytes measured, or for ALT, AST, or creatinine (data not shown).

Symptoms. Analysis of self-reported symptoms is shown in Table 6. The symptoms that subjects reported to be most consistently increased by the herbal *vs* the placebo treatment were dry mouth, heartburn and insomnia. These three symptoms were significantly different at each time point after baseline. Both dizziness and difficulty concentrating were higher in the herbal treatment group than the placebo group prior to treatment and these differences persisted at week 4 and month 3 for difficulty concentrating, but ceased to be different after week 4 for dizziness. Placebo subjects

Table 5 LOCF analysis of blood chemistries[a]

		Group				
		Placebo X±s.d. (P-value)[b]		Herbal X±s.d. (P-value)[b]		
Measure	Study period	mmol/l	mg/dl	mmol/l	mg/dl	P[c]
Total cholesterol	Baseline	5.34±1.22	211±48	5.11±1.04	202±41	0.203
	Final	5.27±1.22	208±48	4.94±0.96	195±38	0.082
	Change	−0.07±0.53	−3±21 (0.23)	−0.17±0.58	−6±23 (0.03)	0.404
LDL-cholesterol	Baseline	3.49±1.06	138±42	3.24±0.86	128±34	0.132
	Final	3.49±1.06	138±42	3.04±0.84	120±33	0.007
	Change	0±0.43	0±17 (0.84)	−0.24±0.51	−8±20 (0.0007)	0.013
HDL-cholesterol	Baseline	1.3±0.4	52±14	1.3±0.4	51±16	0.841
	Final	1.3±0.3	51±13	1.4±0.4	54±16	0.278
	Change	0±0.18	0±7 (0.73)	0.1±0.2	3±6 (0.0001)	0.004
Triglycerides	Baseline	2.93±2.03	116±80	3.11±2.63	123±104	0.650
	Final	2.73±1.67	108±66	2.78±2.66	110±105	0.890
	Change	−0.20±1.14	−7±48 (0.20)	−0.33±1.04	−12±41 (0.01)	0.515
Glucose	Baseline	5.0±0.7	91±12	5.0±0.7	90±12	0.592
	Final	5.2±0.4	94±16	4.9±0.5	89±9	0.056
	Change	0.2±0.5	3±9 (0.02)	−0.1±0.6	0±10 (0.68)	0.051

[a]Treatment was a herbal supplement containing 90 mg ephedra and 192 mg caffeine/day.
[b]P-values for within group change from baseline compared by paired samples, two-sided t-tests.
[c]Mean values of subjects in treatment ($n=70$) *vs* placebo ($n=69$) groups compared by ANOVA analysis, followed by pairwise t-tests of baseline and final values and changes from baseline, with alpha set at 0.05.

Table 6 LOCF analysis of self-reported symptoms

	Symptom								
	Acute phase					Chronic phase			
	B	W1	W2	W3	W4	B	M1	M3	M6
Constipation	—	H > P**	H > P**	H > P**	—	—	—	—	—
Diarrhea	—	—	—	—	—	—	—	P > H*	P > H*
Difficulty concentrating	H > P*	—	—	—	H > P*	H > P*	—	H > P*	—
Dizziness	H > P*	H > P*	H > P*	—	H > P*	—	—	—	—
Dry mouth	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Heartburn	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P*
Insomnia	—	H > P*	H > P*	H > P*	H > P*	—	H > P**	H > P**	H > P**
Anxiety	—	H > P*	—	—	—	—	—	—	—
Upset stomach	—	H > P*	H > P*	—	—				

Acute phase: B, baseline (prior to treatment); W1, W2, W4, weeks 1, 2 and 4 after treatment with either herbal (H, $n=69$) or placebo (P, $n=68$).
Chronic phase: B, baseline (prior to treatment); M1, M3, M6, months 1, 3 and 6 after treatment with either herbal (H, $n=66$) or placebo (P, $n=70$).
*$P<0.05$; **$P<0.01$ (repeated measures ANOVA of group by time interaction, followed by pairwise t-tests).
There were no differences between treatment groups at any time point for blurred vision, chest pain, headache, irritability, nausea or palpitations.

reported more diarrhea than herbal subjects at both 3 and 6 month time points. There were no significant differences between treatment groups in self-reported chest pain, palpitations, blurred vision, headache, nausea or irritability at any time point (not shown).

Adverse effects. Reasons for withdrawal from the study are presented in Table 7. The largest reason in each group was subject choice (P, 24; H, 14). This category included subjects who did not want to continue, moved away or had changes in jobs or personal lives that reduced available time. Investigators removed seven subjects from each group for protocol violations (previously undisclosed ineligibility or noncompliance). Fifteen subjects (eight P, seven H) were asked to withdraw from the study for potential adverse effects. These included one subject who had gallbladder surgery (P) and one with elevated serum creatinine (H). All other investigator-requested withdrawals were for cardiovascular symptoms: elevated blood pressure (three P, two H), irregular heartbeat (one P, one H), MFVE (one P, one H), ventricular events (one P, one H), and ventricular runs of five or more (one P, one H). Four additional subjects withdrew from each group for self-reported cardiovascular symptoms—chest pain (two P, none H), 'loud heart beat' (none P, one H) and palpitations (two P, three H). Subjects also voluntarily withdrew for self-reported CNS effects (two P, five H), and other GI effects (one P, four H). The numbers of subjects who withdrew from the study did not differ ($P > 0.05$) between treatment groups for any individual reason or for any of the system categories.

Table 7 Reasons for withdrawal from study by randomized subjects

	Number withdrawing		
Reason for withdrawal	Placebo (n=43, 51%)	Herbal (n=37, 44%)	P-value 0.44
Subject choice	24	14	0.12
Protocol violation	4	4	1.0
Noncompliance	3	3	1.0
Cardiovascular			
Chest pain	2	0	0.50
Loud heart beat	0	1	0.46
Palpitations	2	3	0.66
Elevated blood pressure	3	2	1.0
Irregular heart beat	1	1	1.0
Multifocal ventricular event	1	1	1.0
Ventricular event	1	1	1.0
Ventricular runs of five or more	1	1	1.0
Total	11	10	0.80
Central nervous system			
Anxiety	0	1	0.46
Disorientation	1	0	1.0
Dizziness	1	0	1.0
Insomnia	0	2	0.21
Irritability	0	2	0.21
Total	2	5	0.24
Gastrointestinal			
Bad taste	1	1	1.0
Dry mouth	0	1	0.46
Gastroesophogeal reflux disorder	0	1	0.46
Nausea	0	1	0.46
Gallbladder removal	1	0	1.0
Total	2	4	0.41
Other			
Elevated creatinine	0	1	0.46

Total number of subjects randomized: 84 to placebo, 83 to herbal supplement (90 mg/day ephedrine and 192 mg/day caffeine). Numbers do not sum to total as due to multiple reasons for withdrawal by some subjects. Roman type indicates subject choice or subject self-reported reason for withdrawal. Bold type indicates choice for withdrawal was made by medical and/or research staff.

Discussion

In this study, a herbal preparation containing ephedra alkaloids (from Ma Huang) and caffeine (from Kola nut), administered with diet and exercise counseling for a 6 month period, promoted significantly greater reductions in body weight, body fat and waist and hip circumferences in overweight subjects compared with similarly counseled placebo-treated subjects. Other beneficial effects that accompanied the greater weight loss of the herbal treatment group included decreased serum LDL-cholesterol, increased HDL-cholesterol levels and decreased blood glucose. These beneficial responses observed in actively treated subjects were accompanied by small persistent increases in heart rate (4 ± 9 bpm by office visit and 1 ± 7 bpm by Holter monitor). Small increases in blood pressure (≥ 3 mmHg) were also detected by 24 h ambulatory blood pressure monitor, although not by office assessment. The numbers of subjects removed from the study for potential treatment-related adverse events were similar in the herbal and placebo groups. Self-reported symptoms that were increased in the herbal treatment group were dry mouth, heartburn and insomnia. There was no difference between groups in self-reporting of palpitations or chest pain at any time point.

Body composition-related effects

The increased weight reduction with the Ma Huang/Kola nut combination in the present study is consistent with results from two previous 8 week studies of Ma Huang formulations.[11,12] These results are also consistent with those from studies of synthetic ephedrine/caffeine combinations in animals[16,17] and humans.[6,9,18] Increased weight loss with ephedrine/caffeine combination is attributed to both decreased food intake[19,20] and increased energy expenditure.[17,20]

As in the two 8 week studies, the reductions in body fat, waist and hip circumferences and the favorable changes in serum HDL and LDL cholesterol levels are probable consequences of the greater reductions in body weight in the subjects treated with the Ma Huang/caffeine combinations. It has been suggested, however, that ephedrine/caffeine combinations have specific effects to increase lipolysis and improve blood lipid profile.[21,22]

The greater body weight loss seen in the herbal treatment group here was probably also responsible for the reduction in blood glucose levels in this group *vs* placebo subjects, although this difference was not seen in a previous 8 week study.[11] Several differences between the studies could account for this, including differences in the ephedra/caffeine ratio (70/240 *vs* 90/192 mg/day), in the herbal formulations and in study length (8 weeks *vs* 6 months). Another possibility is that subjects in the present study were more careful to refrain from taking their herbal supplements prior to blood sampling, thus avoiding influence of a possible acute increase in blood glucose in the group taking the ephedra/caffeine combination.[23]

Cardiovascular effects

The effect of herbal ephedrine/caffeine combinations on blood pressure appears to be small, with previous reports of either no increase[12] or small, transitory increases.[11] As discussed elsewhere,[11] these effects on blood pressure are less than those reported with sibutramine treatment.[24] In the present study, no significant change in blood pressure was detected by office evaluation. The only statistically significant increases that were revealed with 24 h monitoring were small ($\leq$3 mmHg) and some blood pressure measures were found to be significantly decreased ($\leq$5 mmHg). Similar acute[19] and transitory[9] increases in blood pressure have been previously described with synthetic ephedrine/caffeine treatment.

The small increases in heart rate of herbally treated subjects in this study are similar in magnitude (4$\pm$9 bpm) to those observed in the previous 8 week study[11] and to those reported following acute treatment with Ma Huang,[25] or with ephedrine/caffeine.[20] Increased heart rate is consistent with the known effect of this combination to stimulate energy expenditure.[20,26] Chronic treatments with ephedrine/caffeine have been reported to have either no significant effect on heart rate[9] or a slower rate of decrease subsequent to weight loss than seen in placebo-treated subjects.[23]

Despite the small statistically significant increases in heart rate observed in this study, there were no significant increases subsequent to herbal treatment in any of the cardiac arrhythmias assessed. The decrease in incidents of bradycardia with ephedra/caffeine is related to the demonstrated effect of this combination to increase heart rate. Although there has been speculation of a link between consumption of low levels of ephedra alkaloids and arrhythmias,[2] the finding of no cause and effect relationship in the present placebo-controlled study is consistent with the lack of any research data linking synthetic ephedrine to cardiac arrhythmias.[27]

Adverse effects

There were no significant adverse effects resulting from treatment with herbal ephedra/caffeine in the present study. Some subjects were asked to withdraw and some withdrew themselves from this double-blind study for potential treatment-related side effects. Analysis upon completion of the study, however, revealed that the distribution of these subjects was almost identical between the treatment and placebo groups.

How can the absence of treatment-related adverse events in this and two previous clinical trials of ephedra combinations (334 subjects in total) be reconciled with the adverse event reports collected by the FDA from users of these products? Possible explanations include coincidence, pre-existing pathology, non-recommended usage and increased individual sensitivity.

In a FDA-sponsored analysis, Haller and Benowitz categorized 140 adverse-event reports based on how likely they believed the reported events to have resulted from the use of ephedra supplements.[2] The difficulty in making such judgements is illustrated by the controversy regarding their conclusions.[28,29] With millions of Americans consuming ephedra-containing products, it is obvious that some number of adverse events is expected each year regardless of consumption of these products. The real question is not whether adverse events occur in a population undergoing treatment, but whether these occur at a rate that is higher than that of a matched, untreated group. This is impossible to determine from adverse event reports alone. The randomized, placebo-controlled trial allows evaluation of cause and effect relationships *vs* coincidental events.

Most clinical trials purposely exclude individuals with pre-existing medical conditions to avoid confounding of results. It is therefore not justified to extrapolate results from such trials to individuals with such exclusionary medical conditions or to extrapolate results beyond amounts or time periods that have been studied. The possibility of unfavorable interactions between herbal combinations and other medications, either prescription or illicit, should be recognized and warning labels present on herbal products should be adhered to.

Some have expressed the theory that adverse event reports may reflect an unusually high degree of sensitivity in a small fraction of individuals.[2,25] Because of the low suspected incidence, this type of sensitivity might not be revealed in a clinical trial, but requires a case–control study of a very large number of individuals.[25] Such a study would be difficult to conduct, but may be the only way to address the question of rare hypersensitivity.

Conclusion

The present study demonstrated significant beneficial effects on body weight, body fat and blood lipids of a herbal Ma Huang/Kola nut mixture (90/192 mg/day ephedrine alkaloids/caffeine) in overweight men and women who were otherwise healthy. Compared with placebo, the tested product produced no adverse events and minimal side effects that are consistent with the known mechanisms of action of

ephedrine and caffeine. Extrapolation of the present findings to usage by individuals with medical complications (diabetes, heart disease, etc) is unwarranted and usage by such individuals is contra-indicated on labels of commercial products. Evidence from three completed placebo-controlled clinical trials of herbal ephedra/caffeine is consistent with that from a large number of studies with synthetic ephedrine/caffeine. In total, these suggest that herbal ephedra/caffeine herbal supplements, when used as directed by healthy overweight men and women in combination with healthy diet and exercise habits, may be beneficial for weight reduction without significantly increased risk of adverse events. The current widespread usage of herbal products and the increasing incidence of obesity warrant additional clinical trials to confirm and extend these results.

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Appendix I: medical exclusions from the study

Active heart disease, a positive history of palpitations, hypertension (office measurement $\geq$ 140 systolic BP or diastolic BP $\geq$ 90 or ABPM mean 24 h systolic BP $\geq$ 139 mmHg or diastolic BP $\geq$ 87 mmHg), epilepsy, history of mental illness, hyperthyroidism, chronic use of any drug (by self-report or by presence in urine toxicology screen) except oral contraceptives, hormone replacement therapy or synthetic thyroid hormone, active bulimia, known prostatic hypertrophy, pregnancy (reported or detected by HCG testing), glaucoma, active cancer or cancer in remission for $\leq$ 5 y, renal dysfunction, liver dysfunction (ALT, alkaline phosphatase > 2×upper limit of normal), acute or chronic active hepatitis, AIDS, any acute illness within the past 4 weeks, any other chronic illness that might be adversely impacted by concurrent use of the herbal compound, concurrent participation in another research protocol involving diet or any drug use, concurrent participation in a diet program involving severe calorie restriction (800 or fewer calories per day), caffeine intake of 500 mg per day or greater, use of appetite suppressant drugs or ephedra-containing herbal supplements within the last 6 months and weight change of 5 kg or more within the past 3 months.

Appendix II: urine toxicology screen

Amphetamine metabolites, salicylates, phenothiazines, amphetamine class, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates, methadone, phencyclidine, tricyclics, methanol, ethanol, acetone, iso-propanol, ethchlorvynol.