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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRAITON

FOOD ADVISORY COMMITTEE MEETING

ON OLESTRA

VOLUME II

Pages 1 Thru 327

Reston, Virginia
June 16, 1998

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

FOOD ADVISORY COMMITTEE MEETING

ON OLESTRA

Volume II

Tuesday, June 16, 1998

8:00 a.m.

Sheraton Hotel
11810 Sunrise Valley Drive
Reston, Virginia

MILLER REPORTING COMPANY, INC.
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P A R T I C I P A N T S

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Barbara A. Underwood, Ph.D.

Guest Experts:

Rosalie K. Crouch, Ph.D.
Dr. Paul Bernstein

C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN BRANDT: I'm glad to see all of you out this morning so early. At least the sun is shining in contrast to yesterday. We have a busy day today so I hope all the members of the committee got a good night's rest. At this time, I'm going to turn to Dr. Larsen for administrative stuff. There are other words for it, but administrative stuff, nevertheless.

DR. LARSEN: This is, as the members who have been here for awhile know--it's gotten to be kind of a joke--that I always have "administrative stuff." The first item is that all the public hearing speakers have reserved seats over on my right side of the room, and there is a piece of paper on the chair that has your name on it. You should have all filled out a form when you came in that indicates your name, which was pretyped, your affiliation, and it has information about solicitation for your participation at the meeting and whether you're financially compensated.

To the extent we have those forms here, Dr. Brandt will mention that as you get up to save a little time. If for some reason you've slipped through the cracks, there's a blank form at the podium, and please use that form and give us that information before you make your presentation. I think that's all I have on that.

If you are further down the list, I would

appreciate it, and you missed filling out the form, please go back out to the registration desk and do so. At the opening of yesterday's session, I announced that several committee members had been granted conflict of interest waivers. During the early break, Dr. Jacobson asked about the waiver that had been granted, or actually not granted in the sense, to Dr. Clydesdale. Having provided Dr. Jacobson with certain details, it's appropriate also to put that information on the record of this meeting.

In November 1997, Dr. Clydesdale consulted with RJR Nabisco. The subject of the consultation was the fortification of foods and functional foods and involved a single day seminar with some telephone follow-up. For that, Dr. Clydesdale received an honorarium in the amount of $2,000. Now, you may recall that I announced that when we applied for the waiver, our Ethics Division indicated no waiver was required because the honorarium was provided over a year ago, and there's a one-year time frame that we look at as the most critical time frame. So that time frame had passed. That was the most important part.

In addition, had that been within the time frame, the $2,000 is within--is below the level at which we start becoming concerned about what the amount actually is that's provided to a person. So it would have been a waiver that would have been virtually automatic. I just want to put

that on the record.

Each of you was provided yesterday with a letter from Ms. Cindy Rieser at George Washington University. It's come to my attention that some of you may have received a copy which has a blank second page. If you have a copy that has a blank second page, Ms. Rieser provided me with quite a number of copies and I can make sure that you get a copy that has a complete second page.

Finally, during the discussion yesterday, there was a mention of a publication of one of the studies that Procter & Gamble conducted. The reference was to--the citation was to the Journal of Nutrition, page 1726, Volume 127, year 1997. The title of the article is "Assessment of the Nutritional Effects of Olestra on Non-Absorbed Fat Replacement Summary." That has been provided to you. Unfortunately when--I shouldn't say unfortunately, but in the process of trying to clarify what the reference was, Procter & Gamble also provided us with two additional publications out of that journal, and since the trees had already been killed, I decided we'd go ahead and give those to you as well. Apparently that whole supplement deals with the issues, so for your intellectual edification, you have all three.

We've asked Mark Brown from CSPI since he had identified a page out of the many volumes of petition

material that we had received from P&G and he knew where exactly to go in his files to find that page, he kindly is going to be making a copy of the page for us--that was the other reference that he cited--rather than send our folks back to try and dig through and see if they could figure out which one he was talking about. He knew exactly where to go. And so later today, I expect he will provide that to us.

I just want to mention that while we've passed out this material and there has been some discussion of the pre-decisional studies, I want to remind you that the questions before you are about the information and data that we have received since the decision and please remember that when you start to address the question, that's the question that we're asking. That's all I had. Thank you, Dr. Brandt.

CHAIRMAN BRANDT: Thank you very much. Are there any questions from the committee of Dr. Larsen? Seeing none, we will begin with the public hearing. People have signed up. As he pointed out, I have these forms for most people but not all. I just want to tell all of the people who are going to speak to us today that you have three minutes. When you have one minute left, the yellow light will go on. At the end of three minutes, you're going to hear my gavel, which means hush. And the committee will quit listening at that point so please move it along. As I

call your name, I'm going to start the three minutes. So get up to the podium fast. And we will move along. Our first speaker this morning is Susan Parker whose participation was requested by CSPI, and she is receiving no compensation. Go ahead, Susan.

MS. PARKER: This is the correct one. I'm Susan Parker from Springfield, Virginia, to tell you about my experience with olestra. On Memorial weekend, I was out of town in Charlottesville, Virginia. I only say that because I think it really ruined my weekend, but anyway on Saturday, May 23 between 1:30 and two, I ate about a third of a bag of the Wow mesquite grilled potato chips by Frito-Lay. Around four o'clock I started feeling bloated. By 5 p.m., I was extremely bloated. I had indigestion. I was belching. I was laying on the sofa. I ended up going to bed by about six o'clock because I felt really awful.

By seven, I was doubled over with severe abdominal cramps and extremely nauseated. That continued throughout the night. I was up and down and I was on a hotel room with no medication. I was retching, but there was no, nothing would come up, just sick. Finally between, somewhere between three and four, I did vomit twice. That relieved some of the symptoms, but I continued with abdominal cramps for most of Sunday, for part of Monday, and I really didn't feel better until Tuesday. I guess all in all, I was in

severe pain and discomfort about 12 hours, and then an additional 24 hours. So I did not know about olestra. I didn't see a warning label on the bag of potato chips. I only knew about it when I got back home and my husband was telling me about some of the symptoms people had. I looked it up on the Internet, and sure enough, I think that's what caused my problems, and I would only hope that with this, that it would either be taken off the market until it is safe for consumers or at least a warning label that would warn people like me that it can make you severely ill. So thank you.

CHAIRMAN BRANDT: Thank you very much. Our next presenter is Ms. Mary Ball from Howard University. She has not signed in. She's not here yet. Okay. We'll move on then. Next presenter is the Honorable Otis Bowen, M.D., former Secretary of Health and Human Services. Dr. Bowen's presence was requested by Procter & Gamble and his expenses are being paid by Procter & Gamble. Go ahead, sir.

DR. BOWEN: I am Otis Bowen, M.D., a physician and professor emeritus of family medicine, past governor of Indiana, and past Secretary of Health and Human Services. My interest is in health and especially in why people do things to themselves when they know full well it is harmful. This includes improper diet and being overweight. Olestra can contribute to health by lowering the amount of fat and

calories in our diet. We are a nation of snackers. Americans are the fattest people on earth. While serving as Secretary of HHS, I developed faith in the FDA's decisions and conclusions because of the rigorous studies before offering any judgment.

In my opinion, CSPI attacks are unfairly undermining the public's confidence in our health authorities. Statements of frequent gastrointestinal disturbances following consumption of snacks made with olestra are incorrect. Gastrointestinal upsets are extremely common without olestra. It is one of the most common reasons for emergency room visits. Indianapolis was a marketing test area. There were a few anecdotal recitations of complaints, but follow-up studies found that the gastrointestinal upsets were not due to olestra.

To satisfy myself, I recently went to the emergency rooms of four of the largest Indianapolis hospitals and the state board of health and specifically inquired if they had noted any increases in ER visits due to gastrointestinal complaints attributed to olestra? One of the ER physician groups also operated ERs of two other hospitals of medium size in central Indiana. In addition, I inquired of numerous physicians in private practice. No ER personnel nor individual physicians could recall any increases.

Indiana's Commissioner of Health, Dr. Richard Feldman, issued a news release during the test marketing of olestra products and said extensive review of new olestra fat-free snack products by the State Board of Health has revealed no health risks for Hoosiers and supports federal approval of the product. Dr. Feldman also stated that he and the State Board of Health dietary nutritionist have reviewed an extreme number of volumes of research on olestra products. He said the review including the approval by FDA reveals the product reflects no significant health risk. He ended by saying from my review of the literature which included information critical of olestra products, I am satisfied that no significant health--

CHAIRMAN BRANDT: Sorry, sir, but your time has expired.

DR. BOWEN: Thank you. I eat them and so do my grandchildren.

[Laughter.]

CHAIRMAN BRANDT: The next speaker is Dr. Victoria Castellanos from Florida International University. Her appearance was requested by Procter & Gamble, and she is receiving travel expenses from Procter & Gamble. Please begin, doctor.

DR. CASTELLANOS: I would like to share the results of two olestra chip studies that I've been involved

with. The first study was conducted in 1994 at Penn State in the laboratory of Dr. Barbara Rolls where I was a post-doctoral fellow.

[Slide presentation.]

DR. CASTELLANOS: The objective of the study was to investigate the impact of fat-free potato chips made with olestra on fat and energy intake. 95 participants were tested in a cross-over design. Each participant had both regular and olestra potato chips for an afternoon snack for ten days. Half the participants had nutrition information and have the participants were blinded to the manipulation. The main dietary finding was that intake of both olestra and regular chips was similar, resulting in a significant reduction in fat intake over 24 hours.

In terms of GI effects, we had a total of 950 subject days on each type of potato chip. That's 95 subjects times ten days on each type of chip. Now I want to remind you that this study was conducted before olestra was approved by the FDA and for the most part before there was publicity about possible GI effects. We found no significant differences in GI effects at a mean intake of 18 grams of olestra per day. So, for nausea, we had three reports for olestra and two for regular. And in diarrhea and GI distress, we had four reports for olestra and nine for regular.

So, in summary, ad lib fat-free chip intake at the level of 18 grams of olestra per day for ten days reduced dietary fat intake without causing any gastrointestinal effects.

The second study is one that I recently conducted in my own laboratory at Florida International University. Hispanic Americans and African Americans have been reported to have higher fat intakes than do non-Hispanic whites and are also at increased risk for certain chronic diseases. I was interested in whether these groups would find fat-free products made with Olean acceptable and whether they're likely to use them and buy them.

In this study, we recruited 189 women from the greater Miami area. The volunteers were given a six ounce package of fat-free chips in regular commercial packaging and four to seven days later we assessed the volunteers' attitudes about the chips. We found that about 80 plus percent of all subjects gave the chips overall and taste ratings of good or excellent. 89 percent of African Americans and other blacks and 58 percent of both Hispanic and non-Hispanic whites said that they probably or definitely would purchase Olean chips.

83 percent of blacks and 67 percent of Hispanic and non-Hispanic whites said that they probably or definitely would serve them to their family. So in

conclusion, in our studies, GI effects were not an issue. Olean products are highly accepted by a wide range of the population and may help people at risk reduce their dietary fat intake. Thank you very much.

CHAIRMAN BRANDT: Thank you, ma'am. Next speaker is Dr. Lawrence Cheskin from Johns Hopkins University. Presence was requested by Procter & Gamble, and he is a consultant to Procter & Gamble.

DR. CHESKIN: Thank you. Members of the committee, my name is Larry Cheskin. I direct the Johns Hopkins Weight Management Center and the GI Division at Hopkins Bayview in Baltimore and was the principal investigator of the theater test you heard about yesterday. I was puzzled by the reports such as the ones you heard just a little while ago of individuals noting GI effects after olestra and knew that the only way to really decide whether these were something to be concerned about was to perform a controlled double blind trouble. So I proposed to P&G that we do just that. I'm sorry I was not able to be here yesterday to present the results of the study.

[Slide presentation.]

DR. CHESKIN: I understand, though, that there was some discussion about the potential for olestra to cause digestive effects on the same day of consumption, and this was based on the other study you heard about, the six week

home consumption study. However, analysis of that study is confounded because that study was really not designed to look at same day effects. The acute theater study, though, was designed specifically to look at the potential of olestra to cause effects after a single, very precisely timed eating occasion, and I would like to point out that 81 percent of the calls to toll-free lines are after single eating occasions with fairly modest amounts of olestra.

In fact, what we found, the actual results of the study, was that the olestra group had a lower rate of GI effects than the full-fat chips, 15.8 compared to 17.6 percent in the full-fat group. There was some discussion of the power of the theater test, and what we have, the advantage now is having the results of the study. Using those results, we can calculate what the confidence intervals are around the difference that we found, and if you take a look at this transparency, based on the actual findings, we can be 90 percent confident on the left-hand side that there is a one percent or lesser difference between olestra and full-fat chips, and 95 percent confident that there is a two percent difference, and 99.9 percent confident that there is less than a five percent difference in overall GI effects.

The pre-study power calculations are of less value after the fact. People should not discount the value of the

study which I and many others worked very hard on. I'd also like to comment briefly on an underappreciated finding of the theater study. Despite consuming less than half the calories, the olestra group was just as filled as the full-fat group, and this finding has been replicated and very recently published a week ago by Dr. Jim Hill, and there was very little caloric compensation over a much longer two-week period, and for those reasons I'm very hopeful that use of fat substitutes like olestra will be of benefit to the people I see everyday who are struggling to control weight problems or control cholesterol levels. Thank you.

CHAIRMAN BRANDT: Thank you, sir. Our next presenter is Ms. Terry Crowder, whose presence was requested by CSPI, and she is receiving no compensation.

MS. CROWDER: Hi. My name is Terry Crowder. I'm a criminal justice student at the University of Maryland. I had the Ruffles potato chips that contain the Olean in them. I had about ten chips one day and about three hours later, I actually had it with dinner. So I went to sleep. About three hours later, I had to go to the bathroom really very urgently, and I had runny diarrhea. I didn't realize that the Olean was causing this. Actually about three hours later again, I had to get back up and I had runny diarrhea again. The next day I had about ten more chips with dinner. Again, all through the night and through the morning, I had

runny diarrhea. About three or four days after the first chips I ate, I had severe abdominal pains. From the first day that I had the chips, my symptoms lasted about seven to eight days. Again, at the time I did not know that it was caused by the chips until a week later did I actually find out that olestra was actually causing my pain and the diarrhea. I read the warning label on the back of the bag, and it says that you can get abdominal cramping and loose stool. Well, loose stool is not diarrhea. I had severe diarrhea. I mean I had to keep going to the bathroom every three or four hours, during classes, during work, while I was asleep, and I just believe that even if you're going to keep it on the market, then there should be a better warning label. Just because, you know, a lot of people don't realize what this can cause.

Also, if this spreads wider usage for Olean, then those of us who have a sensitivity to it, you know, we're going to have to be very vigilant about what we eat because we don't know if we're going on that picnic if they cook the, you know, chicken in the Olean or if they're putting the potato chips out and if they have Olean. So just, you know, I thought you want to take into consideration that a lot of us have a sensitivity to this. Thank you.

CHAIRMAN BRANDT: Thank you very much, Ms. Crowder. The next presenter is Dr. Steven Czinn from Case

Western Reserve University. His presence was requested by Procter & Gamble, and he is receiving travel expenses. Please begin, sir.

DR. CZINN: Thank you very much. My name is Steve Czinn. I'm an associate professor of pediatrics in the Division of Pediatric Gastroenterology and Nutrition at Case Western Reserve University. I was originally asked by Procter & Gamble to participate as a member of a scientific advisory committee to evaluate the safety of olestra. Subsequently, I was asked to participate as a member of the Passive Post-Marketing Surveillance Advisory Panel, which, as you have already heard, meets quarterly to review consumer generated reports of alleged adverse events associated with the ingestion of Olestra containing snacks.

My role is to pay specific attention to consumer reports generated by children. Recognizing the limitations of analyzing passive surveillance reports, I believe that pediatric reports reviewed as part of this effort do not raise any safety concerns regarding the ingestion of Olestra in children. These conclusions are supported by the large household study presented yesterday. I would like to use my remaining time to review the pediatric data from the six-week household home consumption study, if I can have the first slide, please.

[Slide presentation.]

DR. CZINN: With respect to children age two to 12, and you can see them listed in the columns on the far left, fully 70 percent of children in both groups but more specifically the lesser group never had any symptoms during the 42 day study despite consuming generous amounts of olestra snacks which can be seen on the next slide.

The consumption data for the 442 children eating olestra chips and the 443 children eating regular triglyceride chips is shown in the top half of this slide. The data is quite comparable with regard to the number of eating days, the total amount of olestra chips eaten, and the amount eaten per day. When one looks at the general category of GI symptoms, and these are listed in the bottom left-hand panel of this slide, whether you look either at any GI symptoms or the specific symptoms listed, cramping, gas, bowel movements or loose stools, no increase in symptoms is seen in the olestra group as compared to the control group.

In addition, household contacts had the opportunity to write in other complaints not listed. Of interest is the fact that the control group had far more children reporting symptoms of constipation, a common GI complaint for which parents often seek medical advice. The lack of constipation in children ingesting olestra snacks was viewed by some as a positive side effect.

Finally, as you can see in the lower right hand panel of this slide, regardless of the GI symptom noted, there was virtually no impact on the child's activities. In conclusion, this study along with passive surveillance data does not appear to raise any safety concerns for children eating olestra savory snacks. Thank you.

CHAIRMAN BRANDT: Thank you, sir. Whoever is responsible for that light up there, please turn it off because it is interfering with seeing the slides, which is what we're here. Who is responsible for that light? Get it turned off, please. Thank you.

Our next presenter is Mr. Thomas Devlin, who is here of his own volition. Please begin, sir. He is not being compensated by anyone.

MR. DEVLIN: Hello. My name is Tom Devlin, and I live in Virginia. I am 44 years old and finding that it is increasingly more difficult to keep my weight where it needs to be so that I can remain physically active and competitive in the sports that I enjoy. I work out or play tennis five to six days per week and I eat a sensible, well balanced diet. Things that I can do to lower my fat intake without drastically altering my lifestyle are very helpful to me. Not long ago, I tried fat-free chips made with Olean and thought they tasted great.

They are as good as the other kinds of chips that

I like but without the fat. I do not even eat ice cream, cookies or candy so chips are my snack of choice. I very much appreciate having chips readily available that are fat free and good tasting. A second important reason for my liking my chips made with Olean is my family. My wife and I are encouraging our children to develop healthy eating habits. The kids eat nutritious well-balance meals and exercise regularly, and they also enjoy an occasion snack.

As a parent, I value the availability of snacks that have a taste that children like and that are low in fat or have no fat content at all. I believe that their avoiding excessive fat intake now when they are young will encourage them lead more active lifestyles and prevent health problems later in life.

In addition, my father has recently been diagnosed with diabetes. He too enjoys chips made with fat-free Olean and I am delighted that they are available to him. I hope that Olean can be used to prepare other foods in the future. Thank you very much.

CHAIRMAN BRANDT: Thank you, sir. The next speaker is Dr. Arthur Frank from George Washington University. His presence was requested by Procter & Gamble, and he is receiving no compensation. Go ahead, sir.

DR. FRANK: Good morning. My name is Arthur Frank. I'm the Medical Director of the George Washington

University Obesity Management Program in Washington, D.C. All of the medical management of obesity involves food restrictions and in one form or another dietary deprivation. This is always difficult. It is particularly difficult when it has to be done in a sustaining way: a lifetime of being on a diet. The obligatory pattern of discretion and deprivation is infinitely more onerous in a world of monumental abundance. More than half of American adults are overweight. They are not those people; they are us.

We all cope with the same culture and we all have complicated lives, but overweight people have a special obligation to function in a state of perpetual self-imposed deprivation. Obese people are thought to have their obesity as a penalty for their misconduct. Our culture does not yet understand obesity as a consequence of abnormal physiology. It blames the victim for the problem and for the failure of the therapeutic intervention. Discrimination is a way of life for obese people in social status, in academic opportunities and in employment options. Should we also add the burden of a special standard of perfection when we consider a food substitute, a substitute that might help people who struggle with this disease?

There should be no expectation that food substitutes will cure the disease of obesity, will enable people to decrease their caloric intake or improve their

health, that it will make them better people, leaner people or impart to them virtue, wisdom or restraint. Why then do we consider this possibility? Why are we here today? Is there value in a product which can make life easier for overweight people who struggle continuously with the deprivation of food restricted diets? It can offer them more choices, can restore to them some of the comfort of food and the companionship that surrounds the eating experience, can diminish the meal time stress that seems such a difficult part of the management of obesity, can do this without adding complexity and rules and limitations which restrict the lives of our overweight patients.

Nothing is easier than to proclaim the virtue of the simple life: to eat less and to exercise more. The magnitude of this struggle is difficult to convey to normal weight people and to those who are uninvolved in the management of obesity, the management of this intractable disease. They do not know how difficult it is to have your life suffused with restraint. Obesity is a killer disease. While we struggle to create sophisticated medical management, we cannot neglect the simple things which do have the potential to make its control more accessible and to make it more tolerable and more sustainable. I do believe that olestra is simply one more tool that can provide more choices for my patients and they do need all

the help they can get. Thank you.

CHAIRMAN BRANDT: Thank you, sir. Our next presenter is Mr. Michael Fumento. Is he here? Okay. He's not here. Next presenter is Dr. William Klish who is from Baylor College of Medicine whose presence was requested by P&G, and he is receiving travel expenses. Thank you very much and please begin, sir.

DR. KLISH: Thank you, Mr. Chairman. My name is William Klish. I'm a pediatrician and specialize in pediatric gastroenterology and clinical nutrition. At the present time, I am a professor of pediatrics at Baylor College of Medicine in Houston, Texas and head of pediatric gastroenterology and nutrition at the Texas Children's Hospital. My credentials also include immediate past chairman of the Committee on Nutrition of the American Academy of Pediatrics. I first became familiar with olestra in 1993 when I was asked to serve on the Scientific Advisory Committee for Olestra by Procter & Gamble. I saw my role on that committee as a child advocate, to review the data on olestra and make sure that it was both properly studied in children and that it was safe for children to ingest.

I am firmly convinced that the substance has been extensively tested in children, as you've seen, and that no significant side effects are seen from it in children. Since I'm also a gastroenterologist, I reviewed the

digestive effects of olestra in both children and adults. Any digestive effects seen after the ingestion of olestra, if present at all, I considered to be trivial and of no greater importance than those seen by ingesting a wide range of natural substances already found in the American diet.

As part of my clinical practice, I run a weight control program for children. This program is one of only a few available for obese children in the United States and is run primarily as a service to the pediatric community. It is a conventional program which stresses behavior modification along with diet and exercise. Recently I have been using olestra chips as one of the allowable foods for snacking. In overweight children, snack foods are a significant contributor to their caloric intake, and frequently are the hardest for them to control.

By my observations, olestra chips had some interesting and helpful properties. Firstly, they were very acceptable to children. Almost all the children like them which is a great advantage for us since chips are a common self-selected snack food in children. More importantly, olestra chips seem to satisfy the children's hunger in a fashion similar to regular chips in spite of the fact that they contain about half the calories. As a result of these properties, olestra chips provide my therapists with an additional tool to help deal with the problem of high

caloric snacking in overweight children.

Overall, I consider olestra to be safe, free of significant side effects and potentially helpful for weight control in children and presumably in adults. Thank you for your attention.

CHAIRMAN BRANDT: Thank you, sir. Our next speaker is Mr. Tim Strachan. Not here. Okay. The next one is Mr. Charles Walstrom, whose presence was requested by Alexandria Hospital Diabetes Center, and he is receiving sample chips it says here. Thank you, sir.

[Laughter.]

MR. WALSTROM: My name is Charles Walstrom. I want to thank the committee for the opportunity to provide comments about my positive experiences with snack foods made with Olean. I'm 52 years old, and I've been diagnosed with Type II Diabetes for ten years. I've been overweight for much longer. When I was first diagnosed with diabetes, my doctor prescribed the diabetes pill Micronase. Three years ago, he changed my treatment to insulin and the diabetes pill Glucophage. For about 20 years, my doctor has been advising me to lose weight by eating more healthfully and becoming more active.

When I was diagnosed with diabetes, his advice about healthful eating and exercise took a more urgent tone. However, even with my best intentions, my willpower did not

win out. My experience has been that once I've fallen to the lure of food temptations, I felt that my diet had been destroyed altogether. Then I'd think maybe I would do better on the next diet. There would always be a next diet. I gave up a four-pack a day cigarette habit 30 years ago. I gave up alcohol ten years ago. Neither of these lifestyle changes were as difficult as losing weight and eating healthfully is proving to be now.

Shortly before I was placed on insulin, my father who had diabetes died of a heart attack while waiting for surgeons to determine whether they would have to amputate his foot above or below the knee. So I know firsthand the consequences of diabetes. Unfortunately, I've inherited not only my father's predisposition towards diabetes but also his approach to food. He taught me the joys of fat and sugar. In my quest to satisfy my tastebuds, I have purchased many fat-free foods. To my disappointment, many are tasteless and are loaded with sugars. Thankfully, this is not the case with the chips made with Olean.

I have found that I can satisfy some of my cravings with these snacks without side effects. These products have given me a measure of hope, a hope that has disappeared over the last 25 to 30 years in my battle with obesity and diabetes. I know products with Olean are not a complete solution to my problem, but they seem to help me

more easily make the lifestyle changes that can give me a healthy future. I am glad I am able to buy these foods and welcome forthcoming products made with Olean. Thank you for the opportunity to provide these comments.

CHAIRMAN BRANDT: Thank you, Mr. Walstrom. Our next presenter is Ms. Dorothy Warner, whose presence was requested by the American Diabetes Association and who has received apparently chips. Go ahead, ma'am.

MS. WARNER: Okay. Good morning. I am going to speak without any notes. I have been a Type I diabetic for approximately 25 years. Many times you find yourself deprived of things that you would like to enjoy, and I think that many times as a diabetic we choose to enjoy the wrong things occasionally rather than all the time. When I tasted the Olean chips for the first time, I found that I did somewhat the same thing that I do with regular potato chips or chips of any type is you overdo a little bit.

I did enjoy them, particularly, the natural flavor, I would say, not the ones that were enhanced with the barbecue or the sour cream and onion. I found that the regular chips were quite flavorful and did not give me any, any what I would consider a bit of a side effect. I did notice with the more flavored chips that there was a bit of an after-taste. I'm not certain. I don't use that many of these types of chips anyway. So I don't know if that would

be a normal occurrence.

I think that they would be quite acceptable for people that want to reduce their fat intake and for people with diabetes that want to do the same thing. Thank you.

CHAIRMAN BRANDT: Thank you very much, Ms. Warner. Next presenter is Dr. John Baron from the Dartmouth Medical School. Dr. Baron's presence was requested by Procter & Gamble. He is receiving travel expenses from Procter & Gamble. Dr. Baron.

DR. BARON: Thank you very much. It's a pleasure to be here this morning. Periodically the International Agency for Research on Cancer, a branch of the World Health Organization, conducts consensus conferences regarding the cancer causing or cancer preventing potential of various compounds that humans may encounter. I chaired such a meeting, which was held in Lyon, France, last December, and I'd like to share the results of that meeting with you. The results have just been published in the last week or two.

[Slide presentation.]

DR. BARON: The 30 or so individuals, scientists who met, recognized that beta carotene is the most studied of the carotenoids with regard to the relationship with cancer. We noted that some experimental studies suggest efficacy in animals or in abstract scientific systems in vitro systems, and there appears to be cancer preventive

efficacy in animals at some cancer sites. Moreover, human epidemiological studies, not randomized studies, suggest that there is an association between beta carotene intake and cancer at several sites, lung, head and neck cancer, and stomach, in a protective sense.

There was some indication that beta carotene may be a marker of food and vegetable intake. And in human trials, there was no evidence of benefit of beta carotene supplementation with regard to cancer at any site and there was some indications of harm. There is a summary of the major trials which have been conducted regarding the preventive potential of beta carotene and cancer, and you see that in all of the trials, there was no indication of benefit and in the lung cancer trials, there were some as yet unexplained suggestion of harmful effect.

The International Agency on Research on Cancer summary then indicated that there is no evidence of preventive efficacy at high doses, inadequate evidence of cancer preventive efficacy at lower doses. And supplementation was not recommended, and beta carotene is not thought to be something that explains the cancer preventive effects of fruits and vegetables.

Similar evaluations of other carotenoids--the chemical names are listed there--resulted in even more inconclusive findings. There is no evidence of human

effect. Again, these carotenoids do not explain the cancer preventive effects of fruits and vegetables. So overall, the conclusion was that the carotenoids may differ from one another in their cancer preventive effects. It is very unlikely that there will be a general cancer preventive effect of carotenoids and either benefits or harm are conceivable from carotenoids.

CHAIRMAN BRANDT: Your time has expired, sir. Thank you very much for being here. Next presenter, Mr. Tim Strachan, whose presence was requested by Mr. Ken Fields. He is receiving no compensation. Welcome, sir. You can begin at any time.

MR. STRACHAN: Hello. My name is Tim Strachan. I'm a 22 year old student at the University of Maryland and involved with the football team there. Generally, I'm recognized as the Dematha High School quarterback that was injured in a diving accident a little over four and a half years ago. I'm a C-5 incomplete quadriplegic with the appetite of an athlete and the inability to work out like one. It's been the last two and a half years that I've had to constantly diet and watch what I eat so it's been nice to be able to have the choice of eating a product that is no fat and half the calories.

Awhile back a friend approached me with the potato chips that you've been talking about, and asked me to taste

them, and at first I was reluctant because I don't normally eat potato chips, but after he told me that they were no fat and half the calories, I decided to try them and I couldn't believe it afterwards how good they tasted. Some of my friends and family also tasted them and couldn't believe how good they tasted.

I've heard in the news media about the warning on the packages, about the digestive problems and such. I personally have not experienced any problems nor has anybody close to me experienced any of those problems. It wouldn't be fair for me to say that I'm speaking on behalf of the entire wheelchair community or everyone who is paralyzed, but it is my experience, and I know that there are other people out there, who would like to have the opportunity to eat a product that is so good but also has no fat and it has half the calories. I thank you very much for approving the product and the chips, and I look forward in the future to be able to eat some of the same or more products. Thank you very much.

CHAIRMAN BRANDT: Thank you very much for being with us, sir. Appreciate your presence. Next speaker is Patricia Bertron, whose presence was requested by Dr. Neal Bernard of the Physicians Committee for Responsible Medicine. She is receiving no compensation. Go ahead, ma'am.

MS. BERTRON: Hi. My name is Patricia Bertron and I'm a registered dietician speaking on behalf of the Physicians Committee for Responsible Medicine. PCRM is a nonprofit organization that advocates preventive medicine through good nutrition and higher research standards. PCRM is deeply concerned about olestra's detrimental effect on carotenoid absorption. Found in many orange and yellow vegetables, carotenoids help prevent cancer, heart disease, stroke and blindness. By inhibiting carotenoid absorption, olestra may, according to the best available evidence, increase the toll of prostate and lung cancer, coronary heart disease and macular degeneration.

The current dietary guidelines for Americans released in 1996 by the U.S. Department of Health and Human Services and the U.S. Department of Agriculture states the antioxidant nutrients found in plant foods such as carotenoids and Vitamin E are presently of great interest to scientists and the public because of their potentially beneficial role in reducing the risk for cancer and certain other chronic diseases. These federal departments found it important enough to include a chart on the bottom of that same page listing some good sources of carotenoids such as dark green leafy vegetables, broccoli, carrots and cantaloupe.

A panel of experts on diet and cancer, convened by

the World Cancer Research Fund and the American Institute of Cancer Research issued a 1997 report, "Food, Nutrition and the Prevention of Cancer: A Global Perspective." It states diets high in carotenoids probably decrease the risk of cancer of the lung and possibly of cancers of the stomach, colon, and rectum, esophagus, breast and cervix.

In a four-week Dutch study published in the American Journal of Clinical Nutrition in September 1995, participants who ate just six potato chips worth of olestra had 40 percent less lycopene in their blood than people who did not. Lycopene, a carotenoid found especially in tomatoes, is a nutrient the U.S. National Cancer Institute and others link with lower prostate cancer risk. Approving olestra runs counter to evergrowing evidence of the benefits of carotenoids. Allowing this indigestible fat substitute to be used in food product misleads consumers. They don't need another fat-free potato chip or cracker on the market. They need positive, accurate, helpful messages about how to eat appropriately emphasizing a diet based on vegetables, fruits, grains and legumes.

Given that 55 percent of American adults are overweight or obese, it's obvious that the abundance of fat-free, low calorie snacks has done little good. According to a study published in 1993 in the American Journal of Clinical Nutrition, participants in a 12 week reduced fat

diet lost their urge to eat for the long-term, but other participants allowed to eat fat substitutes retained their taste for fat.

A final note: it is utterly inappropriate to assume that the potential harm from this chemical product will be obviated by a simple warning label on a food package, stating olestra may cause abdominal cramps and loose stools. Olestra inhibits the absorption of vitamins and some nutrients. The reasonable certainty of no harm standards should ensure a safe food product free of offensive side effects. After all, how many consumers expect to encounter warning label--

CHAIRMAN BRANDT: Your time has expired, ma'am.

MS. BERTRON: Thank you.

CHAIRMAN BRANDT: Thank you for being with us. Our next speaker is Ms. Mary Ball from Howard University. She is here at her own request representing the American Diabetes Association. Please begin, ma'am.

MS. BALL: I am Mary Ball. And I live in Washington. I was 59 years old when I was diagnosed with diabetes. Until then I was able to eat just about anything I wanted to eat. Diabetes changed all that. Suddenly, I had to reduce my salt intake, my cholesterol, and amount of calories and fats I ate. But that was easier said than done. I had to eliminate most of what I ate what I thought

was good. I could not eat fat foods and could only eat bland snack foods. Until now that is. For a few months I have been able to snack on potato chips, again, because of Olean. As you know, those chips are fat-free, and they taste great.

I have eaten lots of chips and I have not experienced any of the problems mentioned on the warning label. I also know many others who have tried the chips and have had no problems at all, but do not just take my word for it. I lead a support group for people with diabetes at Howard University Hospital. 35 to 45 of us meet monthly to talk about how we are living with diabetes. In a small but important way, the fat-free chips have already made it a little bit easier for many of us who live with diabetes. For the first time in years, I can sit down and have a tasty snack once in awhile, but I don't plan on making chips a big part of my diet, but thanks to Olean I now have a choice that includes an occasional potato chip. Without Olean, I wouldn't have that choice.

We still have to eat smart and healthy, eat healthy, but these chips give us one more choice and one more option, an option diabetes had robbed of us. I thank you for the chance to speak to you today. Thank you.

CHAIRMAN BRANDT: Thank you very much, Ms. Ball. We appreciate your being here. The next speaker is Dr. Adam

Drewnowski from the University of Michigan, whose presence was requested by Procter & Gamble and who is being compensated by Procter & Gamble. Turn the lights down, please.

DR. DREWNOWSKI: I'm Adam Drewnowski. I am professor of public health, psychology and psychiatry at the University of Michigan, and director of the human nutrition program at the School of Public Health. My area of research expertise is fat. I have published extensively on the role of fat in the American diet and on the connection between fat consumption and the growing epidemic of obesity worldwide. I'm here to make three basic points. May I have the next slide?

[Slide presentation.]

DR. DREWNOWSKI: The first point is that fat consumption in the American diet has not gone down. This slide that you see sometimes showing the inverse relationship between obesity and fat is completely misleading because here fat consumption is expressed as a percent calories. Next slide. As you see in this slide, fat consumption in grams has been going up steadily since 1976. For women, for all adults, consumption of fat in grams is higher; at the same time we're consuming more calories, exercising less and becoming more obese.

My second point is--next slide--that fat modified

foods do, in fact, work. These data are based on analyses of 1996 CSFII, that is the Continuing Study of Food Intake of Individuals, and have been collected by my colleague Madeline Sigman-Grant of the University of Nevada-Reno. The foods in the analysis were desserts, snacks, cheeses, creams, yogurts, spreads and salad dressings. The subjects are divided into four groups: those who use low-fat foods exclusively; those who adopt a mixed model; and on the extreme those who eat no fat foods, high fat foods, whatsoever; and people over here who select only the high fat options.

Next slide, please. What you see here is that avoiding all high fat foods does work. People who avoided all high fat foods consumed fewer calories and reduced amount of fat in their diet. But there is a nutritional penalty. Avoiding whole categories of foods results in a diet of lower quality.

Next slide, please. When you look at the nutrient adequacy score, you will see that people who are avoiding high fat foods had lower nutrient adequacy score, a mean of 14 nutrients, than people who were using either low fat foods or a mixed model combination of low fat and high fat foods.

Next slide, please. The final point I want to make is if people use olestra appropriately, olestra is, in

fact, a marker for a good quality diet. What you see in this slide is evidence if people do not substitute olestra for fruits and vegetables, then the amount of fat in the diet of olestra consumers is actually reduced by more--

CHAIRMAN BRANDT: Your time has expired, sir. I'm sorry.

DR. DREWNOWSKI: Thank you for your attention.

CHAIRMAN BRANDT: Next speaker is Dr. Barry Halliwell from the University of London, Kings College. His presence was requested by Procter & Gamble, and he is being compensated by them. Go ahead, sir.

DR. HALLIWELL: Good morning, ladies and gentlemen. Thank you for allowing me to speak to you today. Two of the few things that nutritionists are agreed on is that the American public and also the European public would be better off if we all ate less fat and more fruits and vegetables, and I think there is general agreement on that. What there is less agreement is why fruits and vegetables are beneficial? First overhead please, number three. Number three, please.

[Slide presentation.]

DR. HALLIWELL: If you eat lots of fruits and vegetables, you automatically have a high intake of carotenoids and beta carotene and some of the other carotenoids which are important sources of Vitamin A in

humans and that is established. The evidence that they do anything else in the human body is extremely weak. Many studies have confused the effects of carotenoids with the effects of foods rich in carotenoids. It's well known that if you have high plasma beta carotene and you smoke, you're at lower risk of lung cancer, but direct tests of the effect of beta carotene have shown that it's not the protective constituent. In most studies that have shown relationships of carotenoid labels to disease, those have been studies showing that foods rich in carotenoids are protective, not that the carotenoids themselves are protective.

Sheet number two, please. In order to study this more, we've recently conducted a number of studies where we're looking directly at the effects of various constituents of fruits and vegetables on free radical damage in the human body. It's widely speculated that carotenoids are important antioxidants. In fact, what we have found in our studies, and they've been confirmed by certain other groups, that consumption of carotenoids, beta carotene and lycopene specifically in human subjects does not change levels of free radical damage to DNA and other molecules in the human body. In some studies of combined supplementations, there were actually increases in free radical damage. These studies have been done with beta carotene and lycopene. There seems to be no good reason why

other carotenoids should have different effects.

Last overhead, please. And it's really not also to my mind expected that carotenoids are going to be good antioxidants in the human body simply because even in vitro, they are very poor antioxidants. They are much less good than, for example, flavonoids. So overall I think that carotenoids are not important antioxidants. Levels of carotenoids are bio-markers of a diet rich in fruits and vegetables, and it's other constituents of those fruits and vegetables that achieve the disease protecting effect. Thank you.

CHAIRMAN BRANDT: Thank you, sir. Next speaker is Dr. Stephen Kritchevsky from the University of Tennessee. His presence was requested by Procter & Gamble, and he is receiving compensation. Go ahead, sir.

DR. KRITCHEVSKY: I'm here to speak on the state of the epidemiologic literature concerning the relationship between carotenoids and cardiovascular disease risk. In general, results from studies of dietary carotenoid intake suggests an inverse relationship, though findings are inconsistent. Six of seven prospective studies show inverse associations, though in only two instances are these differences statistically significant.

[Slide presentation.]

DR. KRITCHEVSKY: Three cohort studies and two

nested case control studies have looked at serum carotenoid levels and cardiovascular disease risk. In aggregate, these studies are consistent with an inverse association between beta carotene or other carotenoids in cardiovascular disease, three studies reporting statistically significant inverse relationships. Against this backdrop of interesting epidemiologic evidence, four trials which have included beta carotene supplementation have reported no protective effect and possibly an adverse effect of beta carotene.

The trial results were quite a surprise to the scientific community, and the basis for the inconsistency between the epidemiologic studies and the trials is unclear, but suggests that the epidemiologic studies may have been subject to confounding by unmeasured factors. There is experience in a large scale trial of a substance other than olestra that inhibits carotenoid absorption, the lipid lowering drug cholestyramine. In the lipid research clinics, coronary primary prevention trial, total carotenoid levels in the cholestyramine group dropped 25 percent in the first year of the trial. If total carotenoids had a marked effect on coronary heart disease risk, one would expect that cholestyramine would be found to be a less effective preventive agent compared to other lipid lowering modalities.

This slide summarizes 11 cholesterol lowering

trials completed when the LRC data were published. The line is the regression line showing the estimate of the reduction of coronary heart disease mortality associated with a given reduction in total cholesterol based on all trials. The reduction of coronary heart disease events in the LRC trials was exactly that which would be predicted on the basis of lipid lowering alone despite an intervention causing a 25 percent reduction in total plasma carotenoid levels.

Much data has become available in the past few years on the relationship between carotenoids and cardiovascular disease. And based on the consideration of this evidence, I conclude that there is no evidence that increasing beta carotene will prevent cardiovascular disease, though the potential benefit of other carotenoids has not been ruled out. The existing epidemiologic evidence must be considered cautiously given the inconsistencies with the clinical trial data that have emerged.

And finally, the LRC data provides some indirect evidence that reducing carotenoids in the blood a modest amount should not have a marked adverse effect on coronary heart disease risk. Thank you.

CHAIRMAN BRANDT: Thank you very much, sir. Next speaker is Ms. Cindy Pearson from the National Women's Health Network. She is not being compensated, but her organization has received funds from Procter & Gamble.

Please begin, ma'am.

MS. PEARSON: Thank you for disclosing that because I was planning to do it on my own and am proud to follow the disclosure rules very scrupulously. In 1995 and '96 Procter & Gamble gave no strings attached grants to the National Women's Health Network which in both years consisted of less than one-half of one percent of our budget. Otherwise, we are a member supported non-profit consumer health advocacy organization. One of the health behaviors we advocate for is a low fat diet, and in general we're happy to see new low fat or fat free food products become available. It's for this reason that we educated ourselves about Olestra and have taken a public position about its safety.

In 1995, when we testified before this committee, our main concern was about olestra's lowering of carotenoid levels. At that time, it had been demonstrated in controlled trials that in volunteers who ate olestra with every meal, carotenoid levels dropped significantly, and also at that time, there was no direct evidence about what the effect would be on consumers who ate olestra containing products whenever they chose.

At that time, we asked that if the FDA chose to approve olestra that they require prospective studies to determine the effect of olestra on carotenoid levels in

average consumers. And we were happy to see that requirement built in when the approval was announced in 1996. We've had the same opportunity, as probably everyone who has testified, to review the publicly available materials regarding the carotenoid study that will be discussed this afternoon that's funded by Procter & Gamble and is prospective to us as a consumer advocacy group that is science based and looking at what's publicly available. This study appears to be of a pretty reasonable size; 80 percent or 90 percent power isn't fabulous, but it's pretty reasonable.

And we're especially pleased to see that it seems to be designed in a way that will lead to the enrollment of a good number of women, children and people of color, groups that too often aren't studied carefully enough. And we're also aware that because of business decisions to not make olestra-containing chips fully available across the country until this year, that this study is not yet completed. So our message to you today is your work isn't over. We realize that the FDA gave Procter & Gamble a 30 month deadline and that's why the meeting is happening today, but you won't have the full results of the study. So we ask that you extend the deadline, not forget it, that you set a concrete time by which the results of this study must be turned in, and that the FDA go through a public process of

review and discussion of the results of this study.

It's obvious that there is still much to be learned about the effects of carotenoids on human health, but we can't miss this opportunity to find out what these chips are doing to carotenoid levels in average consumers. In addition--

CHAIRMAN BRANDT: Your time has expired, ma'am.

MS. PEARSON: Thank you very much.

CHAIRMAN BRANDT: Next speaker is Dr. Steven Schwartz from Ohio State University. His presence was requested by Procter & Gamble and he is receiving compensation from Procter & Gamble. Please begin, sir.

DR. SCHWARTZ: Thank you. The point of my presentation this morning is to convey that there are many factors that affect the absorption of carotenoids from foods. The efficiency of carotenoid absorption is considered to be relatively low and inversely related to the intake in dietary fat has been shown for some time to be a very critical factor.

[Slide presentation.]

DR. SCHWARTZ: In fact, as early as 1958, a study in vitamin A deficient populations consuming high levels of fruits and vegetables containing carotenoids, it was demonstrated that supplementation with dietary fat and not additional pro-vitamin A carotenoids was required for

adequate vitamin A status.

Dietary fiber, of course, has been shown to interfere with uptake and absorption of carotenoids into the bloodstream, and the type of carotenoid is quite important, whether it is a polar xanthophyll or a non-polar carotene. Also reports have demonstrated interaction among carotenoids for absorption in the particle size. That is the matrix of the food system and the digestibility of that particular particle to release the imbedded carotenoid, as you know, is required.

Just to refresh your memory on fiber, one of the more important studies gave volunteers a control meal with 25 milligrams of supplementary beta carotene as the beatlet form, and the plasma response of beta carotene was significantly decreased when 12 grams of citrus pectin was added to the diet, and after two days, two meals, there was approximately a 50 percent decrease in the plasma response.

Very recent studies have shown that the bio-availability of carotenoids can be altered by food processing. Heat treatment of foods we know well causes the degradation of the plant cell constituents, and this results in enhanced uptake and efficiency of carotenoid absorption.

I want to show you the data of some of our recent work in collaboration with Cheryl Rock. Here you see two groups where we demonstrated the enhanced bio-availability

of beta carotene from processed carrots and spinach relative to the raw carrots and spinach and, of course, the orange bar is the processed group who consumed the pureed and processed carrots and spinach relative to those who consumed the raw fresh state, a much higher significant increase in beta carotene plasma responses.

So just to summarize the points of this very brief presentation, many factors affect the absorption of carotenoids from the diet. The presence of food components such as fiber and fat as well olestra are known to influence carotenoid uptake and plasma response, and food processing methods such as thermal treatments and particle size reduction have been demonstrated to enhance--

CHAIRMAN BRANDT: Your time has expired, sir.

DR SCHWARTZ: --availability. Thank you.

CHAIRMAN BRANDT: Thank you very much. Next speaker is Dr. James Freston of the University of Connecticut. His presence here was requested by himself, but Procter & Gamble is paying his travel expenses. Dr. Freston.

DR. FRESTON: Thank you, Mr. Chairman, and good morning, everyone. I'm James Freston, professor of medicine and clinical pharmacology at the University of Connecticut, where I also serve as director of clinical research. I'm a gastroenterologist. My comments pertain to the olestra

label. Two and a half years ago, Procter & Gamble asked me as the president of the American Gastroenterology Association to conduct an independent analysis of the GI aspects of olestra consumption. I recommended instead that we convene a panel of experts in various areas of gastroenterology, motility, microbiology, physiology, pathology and epidemiology, to evaluate all of the data pertaining to olestra's GI effects.

P&G agreed, and also agreed to our stipulation of publishing the results of our analysis regardless of our conclusions. We did subsequently publish our findings in a peer reviewed journal. We concluded that olestra is, in fact, an inert food additive that becomes a stool additive. As such, it may increase stool weight as was demonstrated in the forced fed eight week studies reviewed by the FDA prior to olestra's approval when olestra was given in three meals a day for 56 consecutive days.

In the more realistic studies of olestra chip consumption, however, such as the theater and home consumption studies that were reviewed yesterday, it wasn't possible to demonstrate an increased rate of adverse events and certainly on cramps or diarrhea. We heard yesterday from FDA statisticians that in the home consumption study, there was a dose related increase in the frequency of bowel movements and a trend toward loose stools. This is entirely

predictable from what we know about olestra's mechanism of action. As I mentioned, it's a food additive that becomes a stool additive. The more one consumes, the more there will be bulking and softening of the stool and a tendency to pass stools more often.

This is exactly what we get when we increase consumption of other bulking agents such as bran muffins. These stool alterations should not be confused with adverse events. As was presented by P&G and the FDA yesterday, the alterations had no impact in terms of inconvenience, medical usage, doctor visits, or even people dropping out from the study. They continued to eat olestra snacks for the full six weeks. This lack of impact is understandable when one looks at the magnitude of the stool alterations in the home consumption study.

FDA showed us that any GI alteration was reported with an increased frequency of just 0.34 days out of 42 days. This translates, of course, into three more days per year of any stool alteration in these hard core olestra eaters who were eating--

CHAIRMAN BRANDT: Your time has expired, sir.

DR. FRESTON: --unlimited amounts of olestra. Thank you.

CHAIRMAN BRANDT: Next speaker is Ms. Lynn Moseley, who is here on behalf of the American Diabetes

Association and is receiving no compensation. Go ahead, ma'am.

MS. MOSELEY: Good morning. I'm a registered dietician and manager of the American Diabetes Association Education Recognition Program. I would like to let you know the American Diabetes Association has received and educational grants from Procter & Gamble in the past. The American Diabetes Association represents the interests of 16 million people with diabetes in the United States. We appreciate this opportunity to present our views on the role of fat replacers and specifically olestra in the diet of people with diabetes.

Food and nutrition play pivotal roles in the management of diabetes. Over the years, the professional section of the American Diabetes Association has convened experts in diabetes nutrition to review scientific and clinical data to develop nutrition recommendations in people with diabetes. These recommendations cover important topics in food and nutrition including protein, total fat, saturated fat and cholesterol, carbohydrates and sweeteners, non-nutritive sweeteners, fiber, sodium, alcohol and vitamins and minerals.

Therefore, it is important for the association to address fat replacers and their role for people with diabetes and health care professionals who care for them.

In November in 1996, the association issued in the Journal Diabetes Care two peer reviewed papers, a technical review entitled "Fat Replacers: The Use in Food and Role in Diabetes Medical Nutrition Therapy" and a position statement entitled "Role of Fat Replacers in Diabetes Medical Nutrition Therapy." The position statement supported the FDA's regulatory and review processes assuring the safety of fat replacers.

The statement concluded with the following language: Foods with fat replacers have the potential to help people with diabetes reduce total and saturated fat intake and may therefore in time reduce the increased prevalence of dyslipidemia in Type II diabetes. However for these foods to have any potential benefit to people with diabetes, people with diabetes must learn to use them appropriately.

This language underscores the bottom line for people with diabetes. We must teach them about making food choices so they can select foods that fit into their individualized meal plans. We must give people with diabetes practical advice to help them live in the real world enabling them to interpret the many messages about food and nutrition they read, hear and see. As a dietician, I specialize in developing individualized nutrition therapy plans for my patients. These plans must take into account

the unique medical, social and lifestyle situations that every person with diabetes brings into my office. I have seen hundreds of people with diabetes. For most of them, modifying the fat content of their diet is important.

For patients who enjoy chips, having the availability of fat-free lower calorie chips made with olestra is an option that helps decrease calories from fat without increasing the calories from carbohydrates. That's really what it comes down to for people with diabetes. Having choices, having the option of no calorie, low calorie, no fat food products available makes it a little bit easier to manage their diabetes. Diabetes is a serious life-long disease. Treating it requires--

CHAIRMAN BRANDT: Your time has expired, ma'am.

MS. MOSELEY: Thank you.

CHAIRMAN BRANDT: Next speaker is Mr. Jeffrey Schmidt, who is apparently here on his own volition and is receiving no compensation.

MR. SCHMIDT: Thank you. Good morning. I'm Jeff Schmidt. I live in Arlington, Virginia. I'm 40 years old. I'm in good health. But my family has a history of heart disease and I'm always looking for ways to stay healthy. I enjoy eating potato chips, but regular chips have too much fat in them so I rarely eat them. Recently, a friend told me to try the new chips made with olestra, and I did. I've

been eating chips made in olestra for a few months. However, I think it's important to eat a balanced diet so I only snack on chips occasionally. I do have one important point.

When I shared the olestra chips with friends, they expressed concern about the warning label on the bag. One friend refused to try the chips because the warning discussed possible digestive problems. Other friends, who should be eating the chips, are refusing to do so because of the label. I haven't experienced any digestive problems from eating the chips nor has anyone I know. In my opinion, the label scares more than it informs. I think the label should be changed so people aren't afraid of trying a healthy alternative. Thank you.

CHAIRMAN BRANDT: Thank you, Mr. Schmidt. We're pleased you were here. The next speaker is the Honorable Louis Sullivan, former Secretary of Health and Human Services, President of Morehouse. He is here at his own request, but he does serve as a consultant to Procter & Gamble. Mr. Secretary.

MR. SULLIVAN: Thank you, Mr. Chairman, and ladies and gentlemen. As you know, we have the most advanced, sophisticated health care system in the world, but we are not the healthiest population in the world. So in spite of the tremendous advances in acute health care, we lag behind

many other nations in the overall health status of our citizens. As you'll recall, in 1990, during my time as Secretary, we released the document called "Healthy People 2000." This document, three years in the making with over 1500 participants from around the country came out with almost 300 recommendations for improving the health status of Americans by the year 2000.

Among those were reducing the incidents of obesity in our population including the reduction in the fat content and the caloric content in our diets. Unfortunately, the mid-decade report published in 1995 showed that in contrast to many of the goals where we were making progress, when it came to obesity, we were actually losing ground, specifically eight percent more Americans are significantly overweight today than in 1980.

Olestra, as you have heard, has been a thoroughly studied product and does represent an option for helping Americans to reduce their fat content in the diet. And as you've also heard, obesity is related to increased incidence of heart disease, diabetes, stroke and hypertension. I believe that this product, which has been thoroughly studied, gives Americans another tool in their efforts to improve their lifestyle, to improve their overall health status. Thank you very much.

CHAIRMAN BRANDT: Thank you, sir. The next

speaker is Mr. Ronnie Bugg, whose presence was requested by CSPI and who is receiving no compensation. Go ahead, sir.

MR. BUGG: My name is Ronnie Bugg. I'm 58 years old, retired from the Army, and I live in Chase City, Virginia, which is about 215 miles from here. And I actually drove 244, took a few bad turns. I left this morning at 4 a.m. as I felt it was in my best interest to be here to speak to you. It was on March 6 that I purchased my only bag of Lays Wow potato chips, and consumed a serving that evening with no side effects.

The same is true for the next day. On Sunday, about 4 p.m., I prepared and ate a salad. The salad was made from a prepackaged medley of raw broccoli, cauliflower and carrots. I decided that since I had consumed so little calories that day to grab the Lays and ate from the bag, consuming the remainder, three servings, 225 calories. That night about 10:30 p.m., my stomach started aching over a considerable area. Those so-called cramps lasted all night and nothing that I tried would give me any relief. About 8 a.m., the morning of the ninth, a terrible urge struck me that I was about to have a bowel movement. At this point, in time to describe what I was experiencing was a soft stool is a gross understatement. A lot closer description would be a fireman bleeding a fire hydrant.

That afternoon I proceeded to the grocery store to

buy another bag of Lays Wow potato chips as I concluded that the vegetables had made me sick. I checked the original display only to find the store was sold out. I inquired and found out more chips would arrive the next day. The cashier asked me if I had noticed the warning label on the back of the bag and I told her no. We both proceeded to the display, picked up a bag of Wow's doritos and I read the label. I point out here that the warning label on a pack of cigarettes covers one square inch of the pack. The label on the potato chip bag is only slightly longer, but it has ten times the surface area of a pack of cigarettes.

I hope that no one at the company or the FDA thinks that by locating the label at the left rear bottom side of the bag would cause most people to readily see it. I would be happy if the product were banned so I wouldn't have to worry about this oil eventually creeping into the restaurant supplies, baked goods and the like. I urge as a minimum--

CHAIRMAN BRANDT: Time has expired, sir.

MR. BUGG: Thank you.

CHAIRMAN BRANDT: Our next speaker is Dr. Leo Galland, a physician, whose presence was requested by CSPI and who is receiving travel expenses from that organization. Go ahead, sir.

DR. GALLAND: Good morning. I'd like to address

this group as a practicing internist with 27 years of experience and someone who has done a good deal of work with patients who have gastrointestinal problems, and I have many concerns about olestra's long-term effects on nutrient absorption and also short-term effects in causing gastrointestinal symptoms. There have been thousands of reports of adverse gastrointestinal side effects attributed olestra, and one of the things that the literature on the relationship between food intolerance or food additive intolerance and symptoms indicates, and my own clinical experience indicates, is that people tend to underreport rather than overreport adverse effects of foods on gastrointestinal function.

Generally, one has to search for the connection. The person doesn't make it himself or herself and therefore I think that these reports need to be taken very seriously. I think that Procter & Gamble's claim that adverse effects attributed to olestra on GI symptoms are coincidence are really astonishing in the light of that, and that these complaints really need to be looked at seriously especially because in controlled studies that have been done, albeit short-term, there was a dose-related association between consumption of olestra and the creation of gastrointestinal symptoms.

Now I'd like to deal with a couple of aspects of

this question of gastrointestinal symptoms. Are they harmful or inconvenient or are they merely the result of stool bulking due to olestra? Well, for the most part the complaints that have been received have involved symptoms that produce discomfort, and in 14 percent of the cases, the symptoms were described as severe. Now this is not merely a bulking effect. This is an impact on a person's state of health, at least short term, and feelings of well-being.

One of the issues that has come up is whether olestra produces diarrhea in susceptible individuals or merely loose stool. Now, the technical definition of diarrhea requires studies which cannot be done easily in any kind of surveillance situation. That is the measurement of water and electrolyte losses in the stool. However, in common medical terminology--

CHAIRMAN BRANDT: Your time has expired.

DR. GALLAND: --the diarrhea refers to loose frequent bowel movements.

CHAIRMAN BRANDT: Sorry, sir, but your time has expired.

DR. GALLAND: Thank you.

CHAIRMAN BRANDT: Next speaker is Ms. Lisa Lefferts, who is representing the organization "Mothers and Others" from whom she receives compensation. Go ahead, ma'am.

MS. LEFFERTS: Thank you for the opportunity to present the views of Mothers and Others for a Livable Planet, which is a national, non-profit, educational organization working to promote consumer choices which are safe and sustainable for current and future generations.

Mothers and Others is very concerned about the high incidence of gastrointestinal effects, impaired absorption of fat-soluble vitamins including carotenoids, and other of the many unanswered questions regarding the safety and long-term public health consequences of olestra consumption, particularly for children, who can consume very large quantities relative to their body weight.

Olestra and olestra-containing snack foods are not what our children need. Mothers and Others respectfully submits that in addition to reasonable certainty of no harm, consideration should be given to the ability of products containing olestra to mislead consumers. Presumably a consumer who chooses a snack food product with olestra is choosing it over a regular snack food product to reduce fat intake and to improve their diet. But is there really any sound scientific evidence to support the notion that olestra makes products healthier or improves the diets of consumers over the long term? We think not.

In fact, consumers choosing these products are heading in the wrong direction from a health and nutrition

standpoint. Health authorities agree that eating more fresh, unprocessed fruits and vegetables and whole grains is the best path toward a healthier diet for the vast majority of Americans. Rather than inspiring consumers to make healthier choices, snack foods low in problem constituents like fat tend to result merely in increased consumption of these generally unhealthy foods, not to mention anal leakage. So consumers end up eating larger quantities of these foods which add little if anything positive to overall nutrition or one's overall diet and health, and in olestra's case may present additional risks.

Manufacturers have succeeded in duping some consumers into thinking that these kinds of fake foods are a healthy response to the increased incidence of obesity and diet-related illness plaguing our country. Sadly, they are not. The decision to develop olestra and olestra containing products can only be seen as a marketing decision that serves manufacturers seeking to increase sales of snack foods, not as a decision which serves the public health. We should expect more from the companies in the business of feeding America.

In the context of labels that can be misleading, it's interesting to recall FDA's interim guidance on the voluntary labeling of milk and milk products from cows not treated with recombinant bovine somatotropin, which was in

February 10, 1994. That guidance stated that quote, "Certain labeling statements about the use of rbST may be misleading unless they are accompanied by additional information."

While Mothers and Others challenged this interim guidance in FDA's decision not to require a labeling of dairy products from rbST treated herds, we certainly--

CHAIRMAN BRANDT: Your time has expired, ma'am.

MS. LEFFERTS: Thank you.

CHAIRMAN BRANDT: Thank you. Next is Mr. Robert Wells, who is here representing the American Diabetes Association. He has received some free potato chips to taste. Thank you, sir.

MR. WELLS: My name is Rob Wells, and I'm 40 years old and have been diabetic for 30 of those 40 years, and just three quick points I'd like to make about these snacks. First of all, as a diabetic, as the lady who is a dietician spoke earlier, your food choices are extremely limited. And this simply gives me another choice. I don't, I'm 40 years old, I'm not married, I don't cook. I use my oven to store out of season clothing.

[Laughter.]

MR. WELLS: It makes sense for me to have as many choices of things to eat that I can get a-hold of quickly. Olestra is an option for that. I don't like to, I don't

like to sit and eat things that I know that are bad for me. Probably the worst thing I can do is sit around and eat sugar cane or pure sugar, but at least with most foods, I can figure out exactly what I need and how I need to compensate for it with insulin. With fat, you can't figure that out, and this gives me a choice of how to deal with that.

The second issue, I've tried them a lot, and really have had no digestive problems at all. I don't have a great stomach. It has given me problems before with other food, but this simply did not. And third, I would just like to urge you to not only consider it for snack foods but for other foods that will allow me to cook things, maybe learn how, maybe, you know, have a burned sweater or something like that. But something that would, you know, add it into cooking oils and salad dressings and the like so that we can sort of expand our food choices. Thank you very much.

CHAIRMAN BRANDT: Thank you very much, Mr. Wells. We have one other person who is currently signing up who had a reservation. We'll wait a minute or so till she gets here. Okay. Here she comes. Our next speaker prefers to remain anonymous. Her presence was requested by CSPI and she is receiving no compensation. Please begin, ma'am.

MS. MARYANNE [ANONYMOUS]: Hello. My name is Maryanne. I'm from Germantown, Maryland, and I work in

quality control. My unfortunate experience with olestra began when I ate approximately three handfuls of the Wow potato chips over a three-day period, April 11, 12 and 13. The first two servings I ate with lunch. The third I ate as a mid-afternoon snack. The symptoms began on the 13th with diarrhea that evening and it didn't stop until three weeks later.

I was unable to eat the entire first week, was suffering from nausea and bouts of diarrhea. The diarrhea lasted approximately seven to ten times per day. By that Saturday I was so weak and exhausted I had to stay in bed. I began to doubt that I had a virus because I did not-- usually when I had a virus, it was over three to four or five days max. I didn't have the usual symptoms of a virus, you know, aches and pains, fevers, that type of thing. I also noticed that if I didn't eat or drink anything, I felt much better. I called my doctor who told me I had to force myself to eat. I was drinking ginger ale and Gaterade and now I began to force myself to eat rice.

But everything came out immediately, coupled with cramps and nausea. I saw my doctor a few days after who told me to stay on Brigg diet. She took some tests. I followed her instructions, but I ate only in the evening so that when I got home, or I would be at home when I got sick. I lost ten pounds. I remember thinking at the time being

worried if I had cancer. I was very worried. I was sick to my stomach. I was exhausted and as miserable as you can imagine.

My doctor also gave me instructions to make a list of everything I had eaten to try to narrow down what was new in my diet, as she diagnosed me as having IBS or irritable bowel syndrome. It was at this point I realized the only thing different in my diet was the Wow potato chips. When I spoke to the doctor's nurse about this over the phone, she asked me didn't I read the warning label, to which I replied what warning label?

I grabbed the bag. I couldn't believe what I saw. Never in my wildest dreams did I ever imagine that I would need to look for a warning label on a bag of potato chips. I never saw it. When I did read the label, I never saw any warning also about possibly getting IBS from eating these. I threw the bag away, warned my friends, my family, and wished I had never bought them.

CHAIRMAN BRANDT: Your time has expired, ma'am. Thank you. Okay. We are through with everyone who has signed up and reserved a place, all of the public speakers. We will therefore at this time take a break. Since we're a bit ahead of schedule, we'll take a 20 minute break. It is --yeah--sometimes I feel better than others--9:32. We will reassemble at 9:52 right on the nose. Thank you very much.

[Whereupon, a short break was taken.]

CHAIRMAN BRANDT: Okay. It's time to begin again. Is Dr. Zorich here? Dr. Zorich has requested a minute or so to correct the record. Dr. Zorich, get to a microphone and you may correct it. Where are you? There you are.

DR. ZORICH: [Slide presentation.] Yes. Thank you very much, and I did want to say that I'd like to apologize to Dr. Brown--are you here? If he's not, would someone please tell him that I formally apologized. Dr. Brown correctly read from a Journal of Clinical Nutrition article that six--he correctly read the article. The problem was that the article was wrong when, and I was talking specifically about the number of people who temporarily stopped eating product. I knew very distinctly that I had talked to somebody in the placebo group. This is the correct data from the actual submissions to the FDA included in the food additive petition. The article that Mark Brown correctly read was incorrect so I apologize to Mark Brown. He correctly read an incorrect quote. This is the actual data. There was one person on placebo. Two out of 74 at 20 and two out of 41 at 32. So that is the correct data, and I apologize to Dr. Brown.

CHAIRMAN BRANDT: Thank you very much, Dr. Zorich. Okay. Okay. We had one person who did not show for the public hearing who is now here. And we will put him on,

assuming that we get his form. Here comes the form at least. Okay. Mr. Michael Fumento is here of his own volition, is receiving no compensation. You have three minutes, sir. Where are you? At least get to the podium and we will begin. You have three minutes to speak. Go ahead, sir.

MR. FUMENTO: Thank you. As the author of the only book that I know of, at least, to treat obesity as a national crisis, The Fat of the Land, I've saluted the Center for Science and the Public Interest for being the only activist group in this country that seems to share this concern. In fact, I belonged to CSPI for a year, but I resigned over the olestra issue. Why? Because I don't understand the group's obsession with this product and its willingness to throw science to the winds over it.

CSPI's methodology, if you wish to call it that, is simple. First, you tell people that olestra should be making them sick. You even provide them with specific symptoms. Then you sit back and you wait for people to eat products with olestra and complain that they had those very symptoms. One obvious problem with this is it doesn't even attempt to consider how many people have consumed the product, sometimes very large amounts in a very short period, and who have had no symptoms.

The other is that just as a drug can have a

placebo effect, you can also induce what is called a no-cebo or auto-suggestive effect. Every drug trial shows people getting headaches, nausea, aching joints, and so forth even when they're in the control group which is taking the sugar pills, not the actual drug being tested. While a large number of symptoms can be caused by auto-suggestion, chief among them is stomach pain and diarrhea. If everybody in this room ate breakfast at the same place and somebody announced, somebody in authority, that the food was tainted with salmonella or E. coli, a large number of people sitting here would, within a few minutes, become queasy, experience stomach cramps, and soon there would be a line outside the bathroom stalls.

Even as olestra chips were being test marketed, CSPI was blanketed the air waves with warnings that olestra would cause all of the nasty symptoms which it then proceeded to ask people if they had. Then CSPI held a press conference to announce, quote, "the more we publicize our interest and our toll free number, the more complaints we learned of."

Well, of course. That's exactly the way auto suggestion and the no-cebo effect work. Had CSPI blanketed the area with claims that olestra caused headaches and joint pains, two of the other most common psychogenic illnesses, there wouldn't have been a sudden outbreak of those. The

only fair way to attest olestra on people--

CHAIRMAN BRANDT: Sorry, sir, but your time has expired. Thank you for being here. All right, ladies and gentlemen on the committee, we have heard a good bit yesterday and this morning from public speakers. All of that is now open for discussion by the committee or questions as you may have them for anybody except the public speakers. Please begin. And Dr. Lamm is going to do so.

DR. LAMM: Is Dr. Freston here?

CHAIRMAN BRANDT: Who are you asking for?

DR. LAMM: Dr. Freston.

CHAIRMAN BRANDT: He was one of the public speakers?

DR. LAMM: Yes.

CHAIRMAN BRANDT: No. You cannot ask him questions.

DR. LAMM: Oh, we can't ask the public. Sorry.

CHAIRMAN BRANDT: Ms. Richardson.

MS. RICHARDSON: Yes. I'd like to know if Procter & Gamble could provide us with a copy of the study that Dr. Castellanos did on the group of Latino and African American women?

CHAIRMAN BRANDT: Procter & Gamble, can you do that? Can you give her a copy? That's all she asked for.

PROCTER & GAMBLE: I spoke with Dr. Castellanos,

and she indicated the study is now being written up, and she would be happy to provide that study to anyone who wishes to see it, if they would provide a mailing address, but it is not available at this time. So she's just sharing the results that she's gotten from the study hot off the press, but it's not written up yet.

CHAIRMAN BRANDT: Put Ms. Richardson on the mailing list for sure.

PROCTER & GAMBLE: All right. Be happy to.

MS. RICHARDSON: Thank you.

CHAIRMAN BRANDT: Do you have other? Okay. Other comments, discussion? Nobody wants to discuss anything? That's strange. Or there's Dr. Benedict. I knew we could count on you.

DR. BENEDICT: Can we address for a moment something that came up yesterday, and that is the relative purity of olestra as it's being shipped and carried about the country? Do you guys do limulus assays for LPS? Do your producers do purity testing before they use it or do you test it before it's shipped? How can we address the possibility that there might be some contaminating agents in the olestra that perhaps could induce an allergic or some hypersensitive response? And I have one more, but I'll wait.

DR. TREIBWASSER: All right. I'm not aware that

we do any specific testing of the oils above and beyond what would be done in the normal commercial supply of any normal edible oil that gets supplied in the supply chain. I believe we apply all the same standards and procedures that we would do with that.

CHAIRMAN BRANDT: Would it be worthwhile to have the gentleman from Frito-Lay talk about anything that they do? Is he still here? He ain't here. Okay.

DR. TREIBWASSER: No, here's here.

CHAIRMAN BRANDT: Oh, he is here. Can you get to the microphone and see if you can address Dr. Benedict's question, please? Where are you? Here he comes. Just find an empty microphone.

DR. DROTMAN: Please repeat the question.

DR. BENEDICT: The question essentially is we were discussing yesterday the possibility of hypersensitivities and allergic responses induced by for lack of a better word contaminants in the form of other things that might have occurred during shipping, and my question was do you test for anything before you use the product after you receive it from P&G?

DR. DROTMAN: No, we do not. We just test for purity. We don't test for contaminants like cotton seed protein or soy protein. Is that what you're asking?

DR. BENEDICT: Yes.

DR. DROTMAN: No.

DR. BENEDICT: That and LPS and other things? And how is the shipping done? Is this tank cars or boxes or what?

DR. DROTMAN: Yes, it comes to us through tank cars.

DR. BENEDICT: All right. Thank you. The other question that I have, and I realize that the immunological basis for asking this question is somewhat shaky, but I feel I must ask it anyway. And that is given that you must have a library of serum samples of individuals who have consumed olestra over longer periods of time, have you given any thought to trying to devise an ELISA assay where you can determine whether there has been any sort of antibody production in response to this? And I know that I asked you a few years ago about M-cells and the pirus patch and potential induction of some sort of reaction, and I'm wondering if you've addressed this question or if you have plans to do that? You can't do T-cell clearly because the cells are dead now, but you could go back and examine patients if you really felt it necessary.

DR. TREIBWASSER: We have not done any further examination of the immunological, potential immunological properties, and I think it's going to be--we're really going to have to continue to monitor the post-marketing

surveillance and see if there is any indication in that that would suggest that's something we ought to go and do.

CHAIRMAN BRANDT: Yes, Dr. Rulis.

DR. RULIS: Yes, thank you. Just as a point of background information, as part of FDA's evaluation of food additives, we do carefully look at the identity and the specifications associated with food additives and olestra was no exception, and we assign essentially the specifications on olestra to be the same ones as for edible oils. And we talked about that in the Federal Register document of 1996, and we included specifications for free fatty acid content, total methanol residues, water, residue on ignition, peroxide value, total heavy metal content, and lead. These are typical things that we look at so there are specifications for purity.

In addition, there was interest in whether or not upon heating if olestra created any specific compounds or in the cooking process if any unexpected residues were formed, and those issues were addressed in the Federal Register. Thank you.

CHAIRMAN BRANDT: Does that answer your question?

DR. TREIBWASSER: Dr. Zorich has one further comment.

DR. ZORICH: Can I add a bit of, I think, what may be helpful on this question? We evaluate thoroughly all of

the calls, particularly when it's a report that we really don't expect. So in reference to allergic potential, I'd like you to be comforted to know that we in addition to looking at them have been working with external experts in the area of food allergy, and specifically Dr. Steve Taylor has been helping us and looking at all of our calls. And Dr. Taylor as he looks at the calls said the majority of them don't even pass the first level of scrutiny because they're first exposure.

CHAIRMAN BRANDT: Okay.

DR. BENEDICT: Yes, thanks. Yes, that's fine.

CHAIRMAN BRANDT: Other comments by anybody on the committee or questions? Comments, questions? Yes, Dr. Clydesdale.

DR. CLYDESDALE: I'd like to just go back to this edible oils that Mr. Rulis brought up and ask him the question. If these tests were not adequate, wouldn't you see problems with every edible oil on the market? Why would one assume that the edible oils for olestra would be any different than the edible oils that we use everyday in every other plant? I guess that's my question to Dr. Benedict as well. I'm not quite sure what that was getting at?

CHAIRMAN BRANDT: Who wants to go first? Dr. Rulis.

DR. RULIS: I can try. I think the question is in

large part a speculation, and I think that there are an infinite number of potential questions one could ask in the history of looking at food additives. We have a certain retinue of questions that are appropriate. You could pose a specific possibility, and there might be some chance that it could happen, but I think based on what we have done in the past, we are fairly, we are quite certain that our specifications for food additives right now are adequate. So I don't--I think the question is speculative, and I think it would be difficult to try to answer it in any closed form.

DR. CLYDESDALE: Well, I guess that wasn't quite what I meant. I meant is there any reason to think of the edible oils used in olestra, is there any reason to think that they would be different in any other way than any other edible oil? Am I missing something I guess is what I'm asking?

DR. TREIBWASSER: Dr. Clydesdale--

DR. CLYDESDALE: Yes.

DR. TREIBWASSER: I think if there were something arising out of the edible oil or out of its subsequent shipment or transportation or anything else, you would expect to see some other kind of allergic responses going on in all kinds of foods all the time.

DR. CLYDESDALE: That's what I'm asking. Yeah.

DR. TREIBWASSER: And we don't see that.

DR. CLYDESDALE: Yeah. I guess I'm wondering am I missing something that is going on in some change in olestra that wouldn't be going, you know--

DR. BENEDICT: Actually the source of the question was that not that P&G studies had turned up anything that looked like olestra was or was containing something that was immunogenic. It was to give us a chance to discuss the possibility simply because it was raised by other people. The number of food allergies and the number of foods to which people are allergic is, of course, as you know, extremely low, and looking at the constituents, the little that I know about chemistry suggests that this would be very little different from anything that's not already being consumed, but I thought maybe we should examine that since it had been raised, and since I'm sort of the resident immunologist, it was incumbent upon me to raise the question.

The first exposure reaction suggests that we don't have some sort of an immunogenic response at least for that because you must be sensitized first and then react later. Long-term responses where someone is sensitized and then has nothing and then later responds is more what we would look for, and I wasn't able to find anything that looked that way. But like blood types, where we're exposed to bacteria

and make antibodies, which then react to red cells, there could be some odd thing that predisposes some people to react to something, but as I said the other day, this is not likely to be highly immunogenic compound. I just wanted to explore it more than I was being critical--unusually so.

DR. CLYDESDALE: I understand. I just was asking if that was occurring, wouldn't you see that in other products made with soybean oil?

DR. BENEDICT: I would have expected, yeah. Probably.

DR. CLYDESDALE: Okay. I was just wanting to make sure I wasn't missing something there.

DR. BENEDICT: Okay.

CHAIRMAN BRANDT: Other comments or discussion by anybody on the committee? Dr. Applebaum.

DR. APPLEBAUM: Dr. Brandt, I have some questions on yesterday's presentations? Are they still open?

CHAIRMAN BRANDT: Oh, yeah, anything we've done up till now is open game or whatever the word is.

DR. APPLEBAUM: But I was looking for Dr. Street, but in the absence of Dr. Street--

CHAIRMAN BRANDT: Don't worry.

DR. APPLEBAUM: Okay. Good. then I'll ask my question. The question has to do with the data collection and specifically as relates to the two types of instruments

that were used in terms of P&G's in terms of the passive surveillance and CSPI's, and what has raised my question is in regards to the last speaker as it relates to auto-suggestion. And I guess my question is whenever surveys are done, at least the active surveys, you're always very careful in terms of how the questionnaires are written so as not to lead the subject. And I guess what I'd like to know from Dr. Street is if she could give her expert opinion on the two types of ways in which the data were obtained?

DR. STREET: Okay. The Procter & Gamble method was more like a clinical method where the person called in and they started describing their symptoms and the people wrote down the symptoms. That's how they collected the data, and then they asked, once they said that they had, for example, cramping or bowel movements, they might be asked further questions.

For the CSPI questionnaire, they had a list of questions so they were asked did you experience diarrhea; yes or no? Did you experience loose stools; yes or no? And so initially I thought, well, this might be suggestive to the person if you have this list. On the other hand, I also thought, well, if they have this list, they might also express some of the symptoms they actually had that they might not report if they were interviewed in a clinical manner such as the fecal urgency, and it would also depend

on the interviewer's style because I think some interviewers probably really probe. Like if you say do you have diarrhea, yes or no, and they might say no, some interviewers might say are you sure that you didn't have diarrhea? And I didn't know what style the interviewers used or how they were trained. So I couldn't get an understanding of that. Does that answer your question?

DR. APPLEBAUM: Well, I guess what I'm getting at is in terms of your opinion in terms of how responses were obtained when the people would call in? I guess maybe going back from my experience in terms of not leading the caller, let me put it that way.

DR. STREET: Well, I tended to think that the CSPI calls were more led. I didn't think of it as auto-suggestion so much.

DR. APPLEBAUM: Okay.

CHAIRMAN BRANDT: Okay. Dr. Lamm.

DR. LAMM: Following up on that question, how did the two questionnaires, if you will, or the formats differ in terms of their ability to capture dummy variables, i.e., symptoms like headache and joint pain, or non-digestive system symptoms?

DR. STREET: Well, the CSPI questionnaire was focused on the GI symptoms. They didn't ask the other questions to there was--they had an other category, but the

only way to look at that would be to look at the individual data forms and there weren't very many reports in the "other" category. So the other method was the interview like a clinical interview so people could report anything that they experienced.

DR. LAMM: And how much non-digestive symptomatology was being reported there?

DR. STREET: Oh, I can show you that overhead again if you want to see it.

DR. LAMM: I'll take your--

DR. STREET: It was very small. It was just under 45 people in that group of 1317 people.

CHAIRMAN BRANDT: Dr. Clydesdale.

DR. CLYDESDALE: Yes, Dr. Street, I had another question. A couple of statements were made yesterday by different people, one saying that the reason complaints went down on some of those charts you saw were that because people were buying less product, but then we saw some sales--that was apparently in one part of the country. But then we saw some sales figures in general where sales had gone up very high while complaints were going down.

Did you--I guess I'd like some clarification on that plus the fact did anybody plot anything like a ratio of sales over complaints?

DR. STREET: Well, Nora showed her plot yesterday.

Do you want her to address that?

DR. CLYDESDALE: I'd like to see that again, if I could. But, no, I saw the sales going up while they stayed the same. But was there any plot where a ratio was plotted of sales over complaints or something like that?

DR. ZORICH: I think we can try to estimate that from the one plot that I had.

DR. CLYDESDALE: Okay. And what was--did sales go down in one part of the country? I mean was that?

DR. ZORICH: I think whenever a new food or a beanie baby or anything you can imagine is introduced, there is initial market interest. Typically if it's anything by Disney, of course, you know there's a lot of interest in the product. Then there was a lot of interest in the olestra products. I think it's fair for your perspective that we had an unprecedented level of interest not only from the people calling us but also from trial. Typically when a new food is introduced, it just kind of slowly gains popularity. In the test markets we had evidence of about 30 percent trial over a very short amount of time, and naturally then if you look at the curves for sales, you could say compared to the first couple of weeks, yes, they are down.

But that is a launch phenomenon, which you would see with any popular introduction. It does not mean I would say--I'm not a marketing person--but I do not believe that

marketing people would say that means sales are going down, that's an adjustment, and then you look instead at cumulative sales taking off, and so I do not believe that Procter or Frito Lay believes the sales went down in any sort of abnormal way, just the normal pattern of market introduction. It would be in the afternoon, the early part of the afternoon talk.

CHAIRMAN BRANDT: Okay, Dr. Clydesdale. Dr. Clancy.

DR. CLANCY: Yeah. I wanted to ask Dr. Street back to not this question but the earlier one, in terms of whether folks were being led or not, besides fecal urgency, t seemed to me that I remembered that from the two types of studies that the complaints were very similar except for that one category. That leads me to think that there wasn't any suggestion or even leading going on all that much. What do you think?

DR. STREET: Well, I think I agree with you. On the abdominal complaint and the diarrhea, those were very similar proportions. The part where they talked about discolored stools or staining and that type of thing, that was a higher proportion in the CSPI. But then again it might be that people do not like to report those kinds of symptoms because it's awkward for them. So it may help them to actually have that list, that questionnaire list, to

answer those questions.

[Slide presented.]

CHAIRMAN BRANDT: Okay. Dr. Feinleib.

DR. FEINLEIB: I'd like to concentrate for a moment on the pediatric and adolescent age group. This morning Dr. Czinn and Dr. Klish, I believe, assured us that olestra was safe in the children. I wasn't keeping track of it during the presentations yesterday, but is there any evidence at all, any hint, that some of the trends or occurrences may be different among children and adolescents than it is among the older population?

DR. TREIBWASSER: The answer to your question is no, but Dr. Zorich will get the data here to show you that.

CHAIRMAN BRANDT: Dr. Street, do you want to take a shot at that while you're sitting there?

DR. STREET: I think the home consumption study might show that better, and I was talking to one of our statisticians earlier, and he has some information on that if you'd like to hear from him?

CHAIRMAN BRANDT: Yeah.

DR. STREET: Okay. Here he comes. It's Stuart Chirtel.

CHAIRMAN BRANDT: Why don't all you FDA folks that have presented to us get on up here so that you can respond to questions?

DR. CHIRTEL: My name is Stuart Chirtel, FDA. Yeah, there was no indication of any statistically significant effects in people I looked at 18 and under, and also the effect size, the difference between the Olean and the control were actually the smallest in those groups, and there weren't any statistically significant differences for the variables that I looked at. I yesterday concentrated on loose stools, more frequent bowel movements and cramping. And in that group, there were no statistically significant differences, and if you actually looked at the effects or the differences between the control and the Olean group, they were actually the smallest for any of the age groups.

CHAIRMAN BRANDT: Go ahead, sir.

DR. FEINLEIB: I don't even know whether there is within our purview, but I'll try it. In these studies--

CHAIRMAN BRANDT: I'll tell you. Don't worry.

DR. FEINLEIB: In these studies, is there any information that might guide your marketing or advertising strategy as it pertains to children and adolescents? Particularly why would one advocate in any forum that any younger people should use this fat substitute?

CHAIRMAN BRANDT: Well, that's marginally within our purview so I'm going to allow it, just because you're an old friend mostly. Anybody want to tackle that? You all had a pediatric gastroenterologist running around loose

awhile ago. Maybe they could try to help us with that. Help, help.

DR. CZINN: Could you restate the question?

DR. FEINLEIB: I'm getting at the point where if this is out for public consumption, what would be the concern or maybe on the other side reason for favoring use of this product by young people?

DR. CZINN: I think both myself and Dr. Klish may have alluded to this, and he specifically may be able to make a more compelling case, but obesity in the United States has reached epidemic proportions, and when you look at adolescents and teenagers, the data suggests 15 to 20 percent of adolescents and teenagers are classified as obese, and there is also good data to suggest that the obese adolescent or teenager of today will become the obese adult of tomorrow. So that on those grounds alone, if there is a way we can impact on this major health care concern for children, adolescents and teenagers, I think we may be providing a tremendous public service.

So that might be one way, and I'll turn the microphone over to Dr. Klish and let him add his comments.

DR. KLISH: I agree with those comments.

CHAIRMAN BRANDT: Please identify yourself.

DR. KLISH: Dr. William Klish. I doubt that pediatric age group children are going to be a target for

marketing of this product. However, my concern always was that, you know, we know that children are going to ingest this product, and that's why I originally became involved in advising Procter & Gamble over it. However, since I've had more experience with this product, I think there are some useful uses of it in children, particularly as Dr. Czinn said in the overweight child. I've been using it now for, oh, probably about four or five months in my weight control clinic, and it's very helpful as a substitute snack food for children that are overweight in dealing with their problems.

So that would be if you were going to pick a pediatric population, you know, the one population that one might target.

CHAIRMAN BRANDT: Okay. Dr. Czinn was the previous speaker. Would you just go up to the microphone and identify yourself.

DR. CZINN: I'm Steve Czinn, a pediatric gastroenterologist at Case Western Reserve University, the previous speaker.

CHAIRMAN BRANDT: Okay. Thanks. That will take care of it for the transcriber. Okay. Does that answer? Okay.

DR. FEINLEIB: It does, but it leads to another one, another question. Can you suggest or do you have any plans for any special surveillance activities among younger

people to see whether, in fact, it affects dietary habits, weight gain, or whether it is in any sense efficacious but more so are there any early warning signs that might show up in the young population?

CHAIRMAN BRANDT: Let me just remind you and everybody on the committee that the benefit of this substance is not within our purview. Whether or not it helps clinically in treating obese adolescents or kids is interesting but not relevant to what we've been charged with dealing with. Our issue is harm, not benefit. So we can't talk about that.

DR. FEINLEIB: Well, how about surveillance to try to attempt to detect as early as possible if there is a potential harmful effect?

DR. TREIBWASSER: This afternoon you'll see the active surveillance program, which indeed includes children as part of the population that's being surveilled.

CHAIRMAN BRANDT: Okay. Dr. Chassy.

DR. CHASSY: Yeah. I'm a little bit like Fergus Clydesdale here. I'm not sure I understand what's going on, going back to the question of leading responses, by the two different interview techniques. It seems to me, and maybe I'm missing this, that that's not really the question. Once somebody has called in, that's a pre-selected group of people that have some kind of symptom or reaction or they

wouldn't be calling in, and the two survey techniques are not the point. I thought what the speaker was trying to ask or suggest was that the community had been exposed to a advertising campaign by CSPI that suggested to people that they might have these kinds of symptoms and whether that didn't predispose people to call in and sort of bias the sample. It wouldn't be a good social science research technique certainly to do that, and I think that's what we were asking Dr. Street to comment on, whether it was that climate would have had an effect on these results rather than the actual interview technique themselves?

CHAIRMAN BRANDT: Dr. Street, do you have any comment about that?

DR. STREET: I don't really feel qualified to answer that.

CHAIRMAN BRANDT: Okay. There's your answer. Go ahead, sir. Do you have some other? No. Dr. Wang.

DR. WANG: I just need some clarification where there were reported illness where Dr. Klontz reported there were 21 consumers, and he reviewed the medical information and identified that three were olestra related, and I want to know the age group of those three?

CHAIRMAN BRANDT: Okay. We're talking about the clinical findings on the basis of the medical record, and here he is. Identify yourself, please.

DR. KLONTZ: Karl Klontz here. Yeah. The three individuals who--you're talking about the medical records that were received. As I recall, as I recall, all three were adults. I have to go back and check, but that's the best as I remember now.

DR. WANG: Okay. Dr. Klontz, here's a follow-up. After you reviewed those records, you were convinced that they--I mean these are from the medical records that you have ruled out that it could be any other type of disease associated?

DR. KLONTZ: No, you really can't do that from a medical records standpoint. You've got this limited body of information. In fact, sometimes it's just, it's cryptic in nature. In fact, you see a few lines of physical exam, a few lines of history, and a very brief assessment, and so I think it's impossible to say from that short of a medical record that you've ruled out other possibilities.

DR. WANG: Thank you.

CHAIRMAN BRANDT: Dr. Potter.

DR. POTTER: Question has been asked. Thanks.

CHAIRMAN BRANDT: Oh, okay. Dr. Underwood.

DR. UNDERWOOD: I'd like to pursue just a little bit more the issue about children. As I recall the analyses of the data, there was a rather broad age range in there, two to 12, if I'm correct. And there may not have been

enough of the really younger children in the sample to separate them out, but was there any attempt to look at say those under six? And can you tell us about how many children were involved in that age range?

DR. ZORICH: Under six?

DR. UNDERWOOD: Yeah.

DR. ZORICH: I'll have to ask for those numbers to be shared with me. I don't have it off the top of my head. I would like to add that there was no reason, there was no specific or individual incident or indication for us to pursue looking at by a finer slice. And so had that, had something, had there been a grouping, we would have gone that way because we did look for groupings throughout the study, and so on the first cut, there was no particular grouping by age in a smaller segment that caused us to want to look more closely.

DR. TREIBWASSER: There was also nothing within the age range of two to 12 when you examined that whole age range.

DR. ZORICH: That's what I'm talking about.

DR. TREIBWASSER: Yeah, right, right. That would suggest that there might be something in there.

CHAIRMAN BRANDT: Dr. Clydesdale.

DR. CLYDESDALE: Two. One is from Dr. Klontz. I just wanted to ask just to follow up on Dr. Wang's question,

what is implied when you say there were three olestra related cases?

DR. KLONTZ: We got a total of 21 medical records that were submitted to us, and what I did for each medical record was essentially go through it and focus not just on the history and the physical, but then get down to the assessment and see what the physician ascribed to the best of his or her ability, identified in the medical record anyway, what the etiology was, what he or she thought was going on in this patient at the site. And so as I mentioned yesterday, there were three individuals, the medical records for whom in the assessment section suggested that olestra was the etiology as far as this physician was concerned.

DR. CLYDESDALE: So this was not an endorsement by you?

DR. KLONTZ: No, no. I was just, I was just by objective ability seeing what physicians were saying in the assessment.

DR. CLYDESDALE: Thank you. And the second was I waiting to see a slide from awhile back on sales versus--

CHAIRMAN BRANDT: Oh, I haven't turned it off. Sorry. I thought you had gotten all you wanted.

DR. CLYDESDALE: Sorry, Mr. Chair.

CHAIRMAN BRANDT: Here it is.

DR. ZORICH: This is Pringles--

CHAIRMAN BRANDT: Ah, ah, ah. That's a reflex with me. I'm sorry. Only when I come to these meetings, however. I don't usually yell at home.

DR. ZORICH: And it's just a reflex with me to get out and start talking about my data. So--

[Laughter.]

DR. ZORICH: Sorry. [Slide presentation.] This is the Pringles data. I also--Dr. Drotman was kind enough to give me the Frito data. I think what you can see is--we could probably make some calculations here based off of the cumulative sales. Here you actually have a very small percent of your sales while you have a majority of your calls, and then you could continue probably to make, to ratio that throughout, and I would say that it's, the majority of the calls are before you have the majority of the sales. I think the same thing was shown by Dr. Drotman from Frito-Lay for their products. Let's move it over here to the beginning.

This a cumulative report so most of the calls are occurring here, and this just shows that the incremental calls are here very shallow. So most of the calls are here, and then you see the cumulative sales.

CHAIRMAN BRANDT: Okay. I have one question to ask. Pardon me, Dr. Fennema, but that has to do with some of the testimony we've heard from consumers. I mean it's

been awhile since I practiced medicine, but I still remember a few things here and there, and they sound very much like GI infections, and yet I've heard nothing about stool cultures on these people, which it seems to me it's the kind of the first thing you'd want to do when somebody comes in, particularly complaining of seven days of diarrhea. Do we have any evidence from the medical records that that's being done?

DR. KLONTZ: The answer to that is we have some information. One patient, in fact, was identified as having costrium dysphysil [?] colitis from stool assays, and that--it's at the end of the medical record--that sort of sealed the case there, as far as I was concerned. This was a toxin mediated illness from a bacterium, but, no, a number of the individuals who reported having diarrhea did not, at least in the medical record, indicate that they had stool cultures, and that is disappointing. I would think that stool cultures would have been done more commonly when trying to get to the bottom line of an illness that had no diagnosis yet pinned to it.

CHAIRMAN BRANDT: I think if we presented some of these as case reports, I think if third year medical students didn't say stool culture right off the bat, they'd be busted. But nevertheless, that's neither here nor there. Dr. Fennema.

DR. FENNEMA: Mine is sort of a follow up of yours in a sense. And my question is that among those people who called in with complaints including those who gave testimonies here today, was any attempt made to collect medical histories on these people? I don't recall that this has been talked about.

DR. ZORICH: Yes. As part of the system that Procter & Gamble had in place, there was a specific part of the interview that focused on the past medical history and current medication use.

CHAIRMAN BRANDT: And what about CSPI? Let me--because they did a questionnaire as well, and we need to hear from what they have to say.

DR. JACOBSON: We asked if there is any concurrent disease like the flu or something else going on, and when people reported hives or some apparent allergic like reaction, we asked if there are other substances, food or other substances to which they're allergic, and in both cases, whether it's GI or hives, occasionally there is some other problem going on. With hives, there was, I think, one person who said she was allergic to synthetic vitamins, and I don't know if that's possible or not. But--and in the case of GI, a number of people, a very small percentage--I don't have the percentage--said that recently had a flu or something else.

DR. FENNEMA : Well, how about Procter & Gamble? Are there data there that would provide any insight to whether these people were especially susceptible to dietary insults or anything of that kind?

DR. ZORICH: Overall no. There was, this is a pretty good representation of the overall population. The percent of people who had hypertension, the percent of people with preexisting other conditions like migraines and so we felt that it was overall a smaller subset of the overall population and nothing that led us to believe that by their disease history, we were seeing an increase of representation from a particular group of people.

DR. FENNEMA: Okay. All right. Thank you.

CHAIRMAN BRANDT: Okay. Dr. Benedict.

DR. BENEDICT: This is just a general question. Is there any reason to expect that for lack of a better phrase Joe or Jane physician out on the street is any better educated about the effects of olestra on patients than the patients themselves?

DR. ZORICH: I would tell you that my personal experience would suggest that there is a mix, and many physicians--we have actually done some quantitative research with physicians trying to--I'm also responsible--we are not talking about it here today--for our medical education and health care professional education efforts. So in order to

understand how I need to do my job, I have to hear from professionals in the health care area.

When we do that, we know that there is quite a bit of, there's a range of knowledge on this topic, and I would like to tell you about a particular event that I think will give you some insight. One of the women participating in the rechallenge study in the Indianapolis area had originally called to describe severe abdominal cramping that she associated with the consumption of the snack products made with olestra. She said these effects actually were quite severe. She was willing, however, to participate in the rechallenge study.

In the third week of the study, driving home from the site, she had the onset of severe abdominal pain, which worsened over the next four days to the point that she was hospitalized. She was in the hospital for a week, had a variety of procedures, and was instructed by her physician to get out of that study because clearly eating those products was very bad for her. After the study is completed when we look at her records, in the first week of the study she ate the Wow snacks and did fine. In the second week of the study, she ate regular potato chips and did fine. The third week of the study was also regular potato chips.

So here's a case where she has an underlying problem that's ongoing. The etiology is not clear. Many

times with abdominal pain, there is not a complete understanding. And there is an attribution by the physician that it had to be these snacks when clearly you can see that her eating the snacks and the coming and going of her symptoms seemed to be random in time. And in that case you have a physician with a discharge diagnosis saying this was olestra, and we did call him later and let him know that her olestra ingestion preceded that by weeks and, in fact, she had been eating regular potato chips.

CHAIRMAN BRANDT: Yes, Dr. Feinleib.

DR. FEINLEIB: I believe the longest period of follow-up we've heard about in any of these studies is about eight weeks. Are there any people who have been followed for more than two months in use of olestra products?

DR. TREIBWASSER: You'll hear today about the active surveillance program which has been surveiling people for a year now and will continue on for several years.

DR. ZORICH: But I think it's also worth mentioning, and this is not a control trial, but a majority of us on the program at Procter & Gamble are enrolled in--I ensure that everyone is in a clinical study if they're eating olestra not in snacks since snacks are the only approved use. Those of us enrolled in one of the clinical programs I have established who sampled olestra in other snacks, we have been in that program preceding approval and

have been eating olestra on a regular basis now for about ten years. So I have an ongoing group of people that I observe regularly who are, you know, have been regular eaters over a decade.

DR. FEINLEIB: Are there any findings about that group?

[Laughter.]

DR. ZORICH: They usually fight over the brownies. That's about the only finding.

[Laughter.]

CHAIRMAN BRANDT: My experience is that's true irrespective of what they're made of.

[Laughter.]

DR. ZORICH: Exactly.

CHAIRMAN BRANDT: Any other questions or comments? I'm sorry. Dr. Applebaum.

DR. APPLEBAUM: Just a couple going back to those 21 that you received physicians' reports on. Were any of those 21 part of the rechallenge study?

DR. KLONTZ: Yes, the one Dr. Zorich mentioned. We got a medical record provided by, I believe, P&G on that woman, and she, as Dr. Zorich mentioned, had in the medical record documented at least two previous, very similar clinical illnesses presenting almost identically, to my knowledge, back in '87, maybe '90, and not only that, but

there was indication that following this particular episode, several months later she had yet another clinical bout that was indistinguishable from the previous three. So it seemed to be a pattern there.

DR. APPLEBAUM: And I'm also wondering was there any effort on the part of FDA to contact the physicians or was it just reading the reports that were submitted?

DR. KLONTZ: No. We made a number of attempts and did actually speak with physicians. The one case that was probably the most intensive in nature was the appendectomy. We were concerned when we saw the pathology report that there was a minimal, quote-unquote "minimal degree of inflammation." And that's what led us to contact the pathologist and then go back directly to the patient and ask for informed consent to get the actual appendix slides shipped to FDA where we had our pathologist review it.

DR. APPLEBAUM: And I guess I'm wondering that in light of the Food Safety Initiative and the Physician Survey, did you ask them why they didn't request stool samples be taken?

DR. KLONTZ: No, I didn't in those instances go back to the physician and ask why stool samples weren't taken. No, I didn't.

DR. APPLEBAUM: I just want--one more question. It has to do, Dr. Klontz, and it was late yesterday so I

apologize for this, but you made a comment in terms of the phenomenon that you see as relates to olestra, you see an effect on the first eating occasion, and then upon rechallenge, you don't. And you talked about it in terms of a phenomenon, and I guess it sparked a question. Have you seen this type of phenomenon? I mean you made it sound as if this was a not a common occurrence, but putting it in the context of a phenomenon just triggered my question.

DR. KLONTZ: I brought, those slides were brought up in the context of the rechallenge study. They were slides that actually dealt with the vitamin, the eight week vitamin restoration study, which you'll recall was eight weeks in which individuals ate zero, ate 20 or 32 grams of olestra per day, divided in three meals each day, and when we looked at the data from that study and actually plotted it out by day, you will see in some individuals that there are streaks of time in which they report having loose stools or diarrhea or abdominal cramps, followed by interludes where they're not reporting those symptoms only to be followed a few days in a row where they are. So I, for the lack of a better word, was describing this as an on-off phenomenon which I believe your report you've referred to.

And my question--the reason I brought that up is if indeed somebody, the assumption in a rechallenge study is often one reports a reaction, rechallenge them, and see if

that reaction occurs, yes or no, like an IGE mediated phenomenon classically, and if the assumption is that, my question is why are we not seeing it every time if somebody is truly sensitive, and so from this eight-week clinical study, you can see some evidence that at least in my mind it suggests to me that some people may be sensitive but not manifest those symptoms every time they're exposed to it. It's a theory. I may be wrong, but I'd love to hear more what other people think about that.

CHAIRMAN BRANDT: Dr. Clancy.

DR. CLANCY: I wanted to ask a clarification of Dr. Zorich about your suggestion that you felt that the complaints you looked at, I assume both groups, were coming from the general population in terms of their health situation, but you didn't mention any kind of GI health. All I heard was hypertension and heart disease and other things, and of course with regard to this product, that would be a special category that we would be very interested in. So did you ask about GI health?

DR. ZORICH: It was an open-ended question about health status so it would have captured any diagnosed or underlying, whatever the person would, a self--these are consumers, of course--but, yes, I didn't just ask about hypertension. It was open-ended and we have complaints from people who self-identify themselves as having irritable

bowel. That's a common complaint in the community, up to about 15 percent by some estimates in females, and we have complaints from people who said they had ulcer disease history or active. So, yes, we did have, but what I'm saying is that it was, as a percentage of the total volume of calls, it was not overrepresented as a percent compared to what I would anticipate in the general population.

DR. CLANCY: But there are people with these kinds of complaints utilizing the olestra products?

DR. ZORICH: Yes.

DR. CLANCY: Thank you.

CHAIRMAN BRANDT: Dr. Hubbard.

DR. HUBBARD: To extend this line of questioning a little bit further, in asking questions of the people that we're calling in, and this would apply to both P&G as well as to CSPI, was there any attempt to ask whether these individuals had other quote "food intolerances" or idiosyncratic reactions to specific types of foods that may elicit some GI symptomatology, recognizing that when you ask that type of question some caller-ins may perceive that as a way of minimizing the impact of the olestra itself? I mean was there an attempt to ascertain whether these individuals had experiences to other foods as well?

DR. ZORICH: We specifically asked that for all the callers and test market and had a very mixed

representation and had people ascribing, saying that they had food intolerances from everything that you have typically heard of to things that you probably haven't yet heard of. So we didn't really see any particular pattern. In addition, we had a better look with the rechallenge people we could actually put them, so to speak, under a microscope. They were kind of with us for the four weeks of the study, as a subset of the overall group of callers. And in that group, we did not actually identify a group of people who viewed themselves as having an array of food intolerances.

CHAIRMAN BRANDT: Let's ask CSPI same question since they had a questionnaire out there, too.

DR. JACOBSON: We asked people about do they have other digestive problems, and we ran into the same range, I think, that P&G did where some people had some active syndrome, some people had had their gallbladders removed some time ago, some people had ulcers, some people said they had an ulcer ten years previously. So they didn't fall within neat categories all the time, but there wasn't a huge preponderance of people with preexisting or former GI problems.

We also asked people who went to the hospital, went to the emergency room, about their--and this gets to your question, Dr. Benedict, about what did their doctor

diagnose their situation as, and typically it was, you know, I don't know. GI problems happen all the time. Usually doctors did not take diet histories along with not doing stool cultures, and they did not raise the possibility of olestra, and most of the people when they saw the physicians didn't link their GI symptom to olestra. Typically, they heard about it from a friend afterwards about the possible link, and then they made the connection. Sometimes they informed their doctor.

CHAIRMAN BRANDT: Okay. Do you have other questions? Doctor.

DR. CHESKIN: Dr. Larry Cheskin. I was the PI on the theater study. I think perhaps a better way to answer the earlier question about whether previous history of GI disease is relevant here is to look at a controlled study, which this was, which represents the majority of people calling up the 800 lines in that it's a single eating occasion, precisely timed in this case, and we did have a subset we asked about, whether there was a history of GI disease, and there was a subset who said yes, and they reported no higher rates of effects after olestra than after full fat, and in fact no higher rate of GI symptoms in general.

CHAIRMAN BRANDT: Okay. Dr. Hubbard, do you have other questions?

DR. HUBBARD: Only a clarification of my question. It wasn't so much as specific GI disease, but I mean many individuals out there do have reactions to certain types of foods and certain--they choose either to live with it or select other options at their meal time. But I mean certain people when they eat Chinese food have GI manifestations. I would not call that a GI disease per se. But it's a reaction that individuals have, and sometimes you don't have any good explanation for that observation.

DR. JACOBSON: We certainly ran into that where some people said they have a variety of foods that they think they're sensitive to. They have gas from beans or whatever. And contrary-wise, there are many people who said I've never been sick a day in my life, I have an iron stomach, I go to Mexico and eat raw food all the time, never had a problem till three hours after eating olestra chips.

CHAIRMAN BRANDT: Okay. Dr. Blackburn.

DR. BLACKBURN: I was interested yesterday in some of the analytical strategies to the GI complaints that seemed to be independent of Procter & Gamble's treatment of the data and Procter & Gamble didn't have--it wasn't on the program for them to respond to those analyses yesterday. I wondered if they were interested in these strategies, whether they provided any enlightenment. I think it was Dr. McCarthy's group that used a curve fitting model to look at

the trends over time and dosage and whether that was of interest to the Procter & Gamble group, and Mark Brown's analysis where he got combined symptom days and suggested that this might be a more sensitive way of looking at these differences. I wondered if Procter & Gamble wanted to react to those contributions.

DR. TREIBWASSER: I think there is one analysis of the analysis that was presented yesterday that we would like to comment on, and that has to do with the analysis that was conducted looking at the temporal relationships in the six weeks study. And we specified in the protocol actually that that was an analysis that we had intended to conduct ourselves. And we did conduct it. [Slide shown.] And what we found was that that analysis is extremely confounded by the fact that most of the symptom days are contributed by the people who are eating the most, and what I have put up here is sort of depiction of sort of hypothetical 90 percentile eater in this study.

And you can see that that individual is eating on 35 or 40 days out of the study and is reporting symptoms on four or five days out of the study. The analysis study was conducted then attempts to correlate a symptom that occurred with an eating day, and as you can see in that kind of an analysis, there is the potential for significant confounding, and we therefore did not rely on this

analytical approach in our analysis of the data, recognizing that it's out there and you can do it, but I think the interpretation of the results perhaps should be examined in terms of the validity of what you really see when you do that.

DR. BLACKBURN: And the curve fitting?

CHAIRMAN BRANDT: Get up closer to the microphone.

DR. BLACKBURN: And the curve fitting; was that?

DR. TREIBWASSER: Curve fitting data. Tom Fellone, will you come up here? We need to look at our curve fitting analysis.

CHAIRMAN BRANDT: Well, I think Dr. Blackburn is also interested in your reaction to the FDA's curved fitting.

DR. BLACKBURN: Yeah, I thought it was the FDA's, yeah.

CHAIRMAN BRANDT: Excuse me for trying to interpret what you said, but I'm delighted I did it correctly for a change.

DR. BLACKBURN: And more succinctly than I would have done it.

DR. TREIBWASSER: I mean I think to be clear I think we certainly agree with FDA's overall synthesis that they arrived at at the end of their examination of our data. I think we are really perhaps in the end we will perhaps

agree to disagree over some of the analytical methods that were used to examine that data, and I brought up one case now. I think we also applied a different curve fitting model in terms of looking for the dose response relationships, and we can show you the model that we used in looking at that data.

DR. FELLONE: Hello. My name is Tom Fellone. I'm a statistician with Procter & Gamble. Like Keith was alluding to, we sort of agreed and disagree on this slightly. It just depends on the method of analysis in terms of the magnitude of the effect.

[Slide presentation.]

DR. FELLONE: I mean what has been stated to date is--let me slide this up top so you can see it--what we've got is in Mr. Chirtel's analysis from FDA, he does a dose response where you look at the magnitude of the effect, and what he does, he had done a Poisson regression analysis. He had done a Poisson regression analysis where you actually model the dose response curve in terms of what goes on. One thing is if you actually do--he assumes in a sense a linear model in terms of a monotonic increasing dose response curve.

We had done similar plots, but had noted that it's not a simple linear response, more of an S-shaped curve, if you will, and nothing really occurs before the median type

consumption, and you get a minor effect out in the end. This addresses both the magnitude of the effect. As you can see on this, there's approximately one day, one more day of symptom reporting in the high end eaters, and it does not increase exponentially or linearly as you get out in the high end consumers.

The point is here there is one symptom day extra which actually if you average that over the entire population of people who consumed the product, that's where we get this .25 or .3 symptom day increase in more frequent BMs in terms of this analysis, and if you go further and actually look at impact, there's no impact, as Dr. Zorich already showed.

The one thing is this scale, someone might argue the scale is deceiving in the sense of we're plotting 20. Why do we do 20? That's about the average number of eating days in the study for people.

Let me blow up the scale and try to examine a little bit of the differences between FDA's analysis and our analysis or our conclusions from this. Okay. The idea, Mr. Chirtel's analysis from FDA is a valid analysis, but it assumes there is a linear or exponential sort of dose response curve. When you do the statistical analysis, you enter a linear term, but in a sense it's on a log scale. So if you convert that back, it's really an exponential type

model which is this curve here, this exponential, which is FDA's original analysis.

If you go in what in our analysis is actually this curve here, which is as we see you get up to maybe two symptom days at some point, and it actually drops off in the high end consumers, and this is, in a sense, it's just a simple local average of all the responses. So you're just doing a smoothing process and you're trying to evaluate the dose response curve where you're at in that consumption range.

The Y label should be total ounces consumed over the study, the zero to 250, which has been seen previously. The issue is if you actually include a second order model, in Mr. Chirtel's analysis, you get a curve that looks like this, which actually comes up and comes back down, which mimics what we've seen in sort of our local averaging or more non-parametric sort of analysis. So I think in the end the point is this model, the actual linear model that Mr. Chirtel proposed fits very well in terms of the bulk of the data.

Once you get out to 100 or so, you're well, you're into the single digits of percent of people that are actually consuming that amount in this trial, and as Dr. Zorich also showed, this is more than what MRCA would predict already in terms of consumption. So you're into--

DR. TREIBWASSER: The symptoms drop off.

DR. FELLONE: Right. And the consequence is this is the magnitude of the effect so it fits well in here, and if you actually do something that tries to examine the data in the very high users, you actually see a decrease between either a Poisson quadratic model or a simple smoothing operation. So I think this sort of explains that you can use various models to do various fits in here, and it's just--it depends on what type of model you would choose to use, where we let the data do the talking with the smooth non-parametric approach to try to explain what's going on in the tail end or the high end users. But in any case, you always see, you never see anything more than about two symptom days and if you relate that back to the entire study, this is where the .25 or .3 symptom days come from.

MR. CHIRTEL: Can I respond?

CHAIRMAN BRANDT: Well, wait a second. Well, wait a second. Rather than get into a debate over which analysis is correct, the answer to his question is you disagree with the FDA's and prefer an alternative solution?

DR. FELLONE: Right.

CHAIRMAN BRANDT: That's the answer.

DR. TREIBWASSER: But in the end, the fundamental conclusions we come to probably aren't very different.

CHAIRMAN BRANDT: I mean if we want to sit and

debate it, why we can, but--

DR. BLACKBURN: Well, I'd very much like to see FDA's response and Mark Brown's response if possible.

CHAIRMAN BRANDT: Okay. That's fine. Get in the microphone, please.

MR. FEINLEIB: Can I ask a question about that slide?

CHAIRMAN BRANDT: Yeah, ask a question about that slide. Put that slide back up there if you would.

MR. FEINLEIB: That last slide.

CHAIRMAN BRANDT: The P&G slide.

[Slide.]

MR. FEINLEIB: Is it possible to calculate conditional confidence limits around those three lines?

DR. FELLONE: Yes.

MR. FEINLEIB: And what would they look like?

CHAIRMAN BRANDT: You're going to have to talk into the microphone. You're not being recorded.

MR. FEINLEIB: What would the conditional confidence limits look like about those three lines?

DR. FELLONE: Okay. What happens is the confidence intervals--I've got another one, but it's not in transparencies--the idea of the width of these, if you can follow this red line momentarily, would look something like this. Okay. [Slide.] This would be about where your

standard error is. It's tight in here, and it actually blows up in this range if you actually do the local smoothing, which makes sense because you have relatively little data out here.

So you've got a relatively tight curve fit. All of these, in essence, all of these fall within the standard error of the other models. So any of these three curve fits would be equally valid in a model fitting process, and the idea is once you get out here, you have an extremely large standard error that you're actually fitting.

The idea being if you actually let the data do the talking out here and do a local average or if you would do the simple bending process and convert that into what's the actual amount or what's the actual number of symptom days in that range, you would see an average which would be somewhere around here if you did the 100 plus total ounce consumers.

DR. LAMM: Could you move that a bit over so we could see the graph, the axis on the left?

DR. FELLONE: The label is number of symptom days and the magnitude of the scale is three, zero to three. The previous graph that I showed was zero to 20, to emphasize people ate about 20 days on average. This actually blows it up so we can see where the subtle differences are between these curves.

DR. LAMM: Could you just explain what the zeros are, why they're underlined? What the difference is between the zero and the plus? I see your curves, but--

DR. FELLONE: Okay. I'm sorry.

DR. LAMM: --I don't understand the underlying data.

DR. FELLONE: This is the placebo. This is the placebo line which refers to the crosses or the plus signs. The plus signs are denoted by--the plus signs denote the placebo group, and those are actually individuals in this study. That says this dot right here corresponds to an individual in the placebo group; because it's a plus, they ate approximately 110 ounces through the entire six week study, and they reported one symptom day of more frequent BM. So on one of those 42 days, they checked the box on the diary forms of more frequent BMs.

CHAIRMAN BRANDT: Okay. Mr. Chirtel, you want to respond, please?

MR. CHIRTEL: Sure.

CHAIRMAN BRANDT: But be sure you're wired up, wired up and turned on. Yes, the last questioner was Dr. Lamm that I didn't identify before he asked.

MR. CHIRTEL: Can you hear me? Okay. [Slide presentation.] This is one of the models that I showed yesterday. The model just described had males and females

combined and I prefer to look at males and females separately. The slopes, the males and females, seem to behave differently. Here we see my model based on household means, my statistical model, and these values are actually means of individuals grouped by consumption, and you can see there really is quite a good fit, and after I presented some of the data to Procter & Gamble a month or two ago, I went back and added a quadratic term to this model just to see what would happen, and it was .06. So it may have some effect, but in addition if you cut off this slope here, you get even a steeper kind of a slope.

But the point is there's clearly a trend here. We didn't see any trends in the control group, and that's why, in a sense, we have control groups. There were not trends in the control group, and no trends for the Olean group or the control group consuming triglyceride labeled or conventionally labeled conventional chips. So there's a trend. The other point--

DR. HARLANDER: Excuse me. Can I ask--this just goes up to the 100, to 100 on the--

MR. CHIRTEL: This group, because as was pointed out, anybody consuming between--this is the mean for anybody consuming over 80, 80 to 250, which is extremely high consumption. As pointed out earlier, this is probably about the median for this study, and it might well be the 90

percentile for the country as a whole, free-living people. So I mean this is very, very high consumption out here.

I want to show this one. The same--this is no statistics on this. This is just a description, but this is what we think is really happening. The control group essentially flat profiles. Half the people in both groups having no symptoms, regardless of how much they're pigging out here. See flat groups. And we see the real--this is what is driving the trend, this increase in the most symptomatic ten percent of individuals, and this is what's causing the mean to sort of move up like this. So that's--

CHAIRMAN BRANDT: Okay. Dr. Brown--is he here? Dr. Mark Brown?

DR. BARTON: Excuse me. This is Dr. Barton. I'd like to say something about the temporal analyses that were mentioned a minute ago.

CHAIRMAN BRANDT: Okay. Let me just find out is Dr. Brown here, Dr. Jacobson?

DR. JACOBSON: I haven't seen him this morning yet.

CHAIRMAN BRANDT: Okay. So we'll have to, you'll have to forego his response, Dr. Blackburn, but go ahead, sir. Again, identify yourself again. I interrupted you and all that kind of stuff in my arbitrary and capricious way.

DR. BARTON: Dr. Curtis Barton, Division of

Mathematics in FDA, Center for Food Safety and Applied Nutrition. [Slide presentation.] Procter & Gamble produced a protocol for this study with a planned analysis method and this is the planned analysis method when they had conducted this analysis and submitted this to FDA. The results of the planned analysis, you can see they found significantly greater more frequent bowel movements, significantly greater gas and significantly greater looser stools.

The temporal analyses that I did found the same thing. All of the analyses that I presented yesterday support and confirm the planned analyses for the study. There are some difficulties and complexities to these temporal analyses and we did a great deal of work trying to sort things out, and the results came out surprisingly clear, the results I produced yesterday, that showed that the effects occurred on days when olestra was eaten. There was a slight increase in those effects if olestra had been eaten the two previous days. And I guess that's all I have to say.

CHAIRMAN BRANDT: Dr. Blackburn, are you satisfied, reasonably satisfied, quasi-satisfied, or something in between?

DR. BLACKBURN: Well, something in between. It would be useful to address Procter & Gamble's claim that the other strategy using the grid in which you compare actual

days that people have symptoms against the days they took the material is hopelessly confounded or as Dr. Brown is claiming it was a more sensitive approach. So if and when Dr. Brown comes back, I would like to have that little point clarified. I think we're getting a better impression here of whether there are or how much symptoms there are.

CHAIRMAN BRANDT: Dr. Askew.

DR. ASKEW: This is for Dr. Zorich or any gastroenterologist that wants to comment. I've been trying to mull over in my mind if it's possible that olestra might possibly potentiate any simultaneous ingestion of food borne pathogen? I'm assuming that olestra does not change the GI transit time. Would it change the exposure of the intestinal epithelium to any food borne pathogens? In other words, would it cause the pathogen to have a greater contact time from the ingest and move it out to the content with the epithelium or anything like that? Has that been considered?

DR. ZORICH: Boy, that's a, I think I would like to ask for some help from any of the people who have a better idea of infectious disease and gastroenterology. I would say that I can't conceive a mechanism by which pathogens would be more virulent by virtue of the fact that you had ingested olestra.

DR. TREIBWASSER: I would just add to that and say we have no evidence from all the previous work that transit

is significantly changed or the GI epithelium is significantly changed or any other aspect of the normal GI physiology or anatomy is in any way impacted by ingesting the compound. So--

DR. ASKEW: How about micellar formation? Is that any change in the micelles that are formed?

DR. TREIBWASSER: Not that we're aware of. Olestra does not participate in micelle formation. Normal dietary fat digestion is unchanged so bio-acid physiology is essentially unaltered in terms of recycle times and things like that so we have no evidence that suggests anything about the normal micellar pathways are in any way altered.

CHAIRMAN BRANDT: Identify yourself.

DR. CZINN: Steve Czinn, pediatric gastroenterologist, Case Western Reserve University. My laboratory has significant expertise in studying certain enteric pathogens, specifically the ones associated with ulcer disease, and as such, with regard to your question, I think all the data suggests that olestra is inert, has no real interaction with the gastric or intestinal epithelial cells and as such, although I have no data to confirm this, it would be difficult to come up with a hypothesis whereby this agent might impact in an adverse fashion on food borne illnesses or other enteric infections.

DR. ASKEW: Thank you.

CHAIRMAN BRANDT: Dr. Lamm.

DR. LAMM: Again, I'm not sure to whom the question is addressed, but I'm still intrigued with the latency, the time of onset from time of exposure to time of symptom report. Could some of your gastroenterologists or others describe the time interval that you've been reporting? What is this consistent with? The infectious disease people will probably tell you for salmonella or such you expect 24 hours; some of your metal toxins, you expect a half hour or so. Someone else had mentioned something about oat bran muffins and what they do to the stools. What are the other experiences that you can reflect on that would place a context into which we should be thinking about this time interval?

DR. ZORICH: I think the first study that I showed yesterday, we looked specifically from the first ingestion, the first time the snacks were consumed, to then the first reports of and the first measurable change in the stool consistency, and what you could see that it was dose dependent. If you're not familiar with normal transit, there is a certain amount--as the digesta traverses the colon, there's a certain amount of kind of back mixing. So in a smaller amount ingested, it will take you actually longer then to have an effect because there is the dilution of the olestra. But at 20 grams a day, eating

consecutively, the effects were not evident until the third day after the first ingestion in this population.

I would also say that based upon a variety of studies that we have done, and as you saw from the eight week studies, many studies, even where we do feed enough to get the sufficient amount to see a dose dependent effect, there is always a lag. So there is a range of transit in the normal population, but the majority of transit is in the one to three day range from when you eat to--

DR. LAMM: I understand, but I'm asking--

CHAIRMAN BRANDT: Into the microphone. Into the microphone.

DR. LAMM: Sorry. I understand that from your studies, but how does this relate to the reports you're getting where most of them, most of your reports occur within a few hours of exposure?

DR. ZORICH: I would say they are inconsistent and that was one of the analyses that was presented by Bob Sandler when he talked about the post-marketing surveillance data looking specifically at the time of onset of the symptoms relative to what would be expected and so they're not, the reports that come in from the 800 line are not consistent with what you would anticipate.

CHAIRMAN BRANDT: Okay. We've got a comment from Dr. Klontz about this issue and then Dr. Jacobson next.

DR. KLONTZ: Dr. Zorich, the point you made, I think you made was in some of the clinical trials, you always saw a lag in reported GI symptoms, and I would like you to clarify that. I've looked at the dose response and the vitamin restoration studies, and in fact in the 20 gram per day group, there are--and let me be specific--in the vitamin restoration study, of the 51 individuals that were on the 20 gram per day group of olestra, there were actually six individuals who reported having diarrhea or loose stools or abdominal cramps the first day.

DR. ZORICH: Yes, and I want you to know that I haven't had time to submit the report because I've always been troubled by those reports. Dr. Klontz and I have--you might pick up from this conversation--have talked about these reports a couple of times. And I was able to identify two of those six people, and I entered them into our rechallenge study, and I found that they were intolerant. And so we do not have baseline data on those people. And in fact one of the people I entered into the rechallenge study basically had symptoms every week. So I think this was just a common symptom reporter, and then the other woman who was in the study, she had symptoms once on Wow and once on triglycerides. So I think without, there was no baseline period in that study. So there were more people in the 20 gram a day group.

There were also some people with reports in the placebo. On a relative basis, what we found was that without baseline, there are people who simply do report more often. So at least on two of those six, I could not confirm that they had olestra intolerance.

DR. KLONTZ: Yeah. I appreciate that. On the other hand, if you look at the placebo group, and you put up the 20 gram per day group, you see a lot more symptoms in the 20 gram per day group suggesting that if this is truly all background stuff, that 20 gram per day group is having a lot more background symptoms. I find that hard to--

DR. ZORICH: No, my point has always been that those people had the anticipated response, dose dependent response, after a lag, and that what we saw early on was not necessarily in the design of that study clearly attributable to olestra, and that's why I went back to rechallenge them because it has never made sense to me.

CHAIRMAN BRANDT: Okay. Wait a minute. Dr. Jacobson, you wanted to respond to this issue now.

DR. JACOBSON: The question about the lag time, when we've talked to gastroenterologists about that, they've had two comments. First is that the transit time varies tremendously between individuals and within an individual, and some of it has to do with full stomach versus empty stomach. And some said time to colon could be as short as

two hours. That's one issue.

The other issue was they said, well, it doesn't necessarily have to get to the colon. It could be causing GI symptoms in the stomach or in the small intestine as well.

CHAIRMAN BRANDT: Okay. We'll move on. Dr. Chassy.

DR. CHASSY: Sorry. It's covered.

CHAIRMAN BRANDT: You've done got yours answered. Dr. Hubbard?

DR. HUBBARD: Just a specific question with regard to your stool composition study. Did any of the people in the--

CHAIRMAN BRANDT: You're going to have to speak up a little bit. I can't hardly hear you.

DR. HUBBARD: Did any of the individuals in your stool composition study report symptoms during the first day?

DR. ZORICH: Yes, and it was comparable to the placebo rate.

DR. HUBBARD: In those that reported symptoms, was there any particular observation made with regard to the chemistries or the studies done on their stool samples?

DR. ZORICH: I have not looked at that specifically on a day by day basis. I have done those

comparisons over the course of the study for symptom reporting and non-symptom reporting, and those differences are seen and they're of the order of about ten to 20 percent differences in terms of stool output, but that's in a composite, not day by day. I hope I didn't need to mention, but, of course, the people in the sorbitol, the first day were seen.

CHAIRMAN BRANDT: Dr. Feinleib.

MR. FEINLEIB: Yes. Getting back to the rechallenge study, I just became somewhat confused. You keep talking about the placebo group and the 20 gram group. This was, as I understand it, a within subject cross-over design. So these are the same people. And what you're analyzing is the period when they're on the placebo and the period when they're on the 20 grams. But they're the same people. Any chronic complainers should have been represented in both periods.

DR. ZORICH: I'm sorry. We have confused you. Dr. Klontz and I went off on a tangent into a previous study conducted in 1992.

MR. FEINLEIB: Sorry.

CHAIRMAN BRANDT: Which is out of bounds, by the way, to remind everybody. I let that go on just because I feel good today and only. Dr. Blackburn.

DR. BLACKBURN: I think we all realize that one of

the biggest problems of this advisory committee is how to deal with the potential for long-term effects, something that's really a massive uncontrolled experiment that's now unleashed. I think Procter & Gamble has done a very commendable job in trying to fill in some of the intellectual gaps that I think we helped identify a few years ago.

But it's pretty hard to fill in the gap of the long-term effects. I would like to--while we've still got the gastroenterologists and fiberologists around, some of them have already left, I'd like to address a long-term, perhaps very remote potential, but have somebody respond to it for me. I talked to my older clinical colleagues who lived in the days when people took a lot--adults took a lot of mineral oil. They abused mineral oil. And they talked to me about lipoid granulomas in the lung and in the mesentery, and metabolic and nutritional syndromes associated with those. We've been assured, and I think we've gotten the data several times, about non-absorbability of olestra, but they point out to me that when you add colase and when you add tween and when you add other agents or you're taking them, that there may very well be regular minimal absorption, though nobody knows about this molecule, I suppose.

And I would just like somebody to respond to that.

How much is absorbed under what situations? Have there been attempts in animals or otherwise to add wetting agents to see how much is absorbed and whether granulomas might be something we'd be facing ten years down the line?

CHAIRMAN BRANDT: Identify yourself.

GRANT [?]: Grant [?] from Procter & Gamble, toxicologist. We did look at the absorption of olestra in quite some detail and, of course, we reviewed that last time. We've also closely followed what's happened with the mineral oils, and clearly the toxicity of mineral oil is directly related to its absorption, and it's very easy to show that you get about a one percent absorption of mineral oils while we were able to go down to see basically no absorption of olestra down to very, very small detection limits, eight times ten to the negative fourth percent of the dose. So even though you can get a gramlotomas reaction from mineral oil, it's because it's absorbed and olestra is not absorbed.

DR. BLACKBURN: Even with wetting agents?

DR. TREIBWASSER: I'm not sure I recall the answer to the wetting agent question, but I seem to recall that we did do some work on tween mediated absorption. We certainly looked at the potential for absorption when you disrupt the GI epithelium, and we did it in a carrageen and induced ulcerative colitis model, and we saw no increased absorption

in that situation where we pretty significantly disrupted the GI epithelium.

GRANT [?]: And we've used some pluronics as well in some of the studies to look at, to increase absorption potential and shown no toxicity effects. Pluronics, a solubilizing agent, detergent.

CHAIRMAN BRANDT: Dr. Clancy.

DR. CLANCY: Yeah. I know this goes back to the discussion that was taking place about a study that was done awhile ago, but I think it's important to, in terms of Dr. Zorich's answer to a question a couple of questions ago, I have a comment about the philosophy of science, and that is I really believe it's important, particularly with these new food additives, to be very careful that despite some reasons for thinking that a particular compound will act always in a certain way, that we stay open to the possibility that, in fact, in some people under certain circumstances we would be looking at different things and not have the answer for why it's happening that way at that time in that person, but not try and explain away or not accept the fact that that is, in fact, the finding, and I think for all of us looking at all the new additives, not just olestra, but everything else, and old ones if we need to, that we remember that theorem from the philosophy of science that says that things can be different.

DR. TREIBWASSER: I very much appreciate that comment, and I think that was one of the reasons why when we began to look at our passive surveillance data that we went outside and found five other people who could look at that data as well and look at with perhaps more subjective or objective views than we might put on it.

DR. ZORICH: And I would say that it was exactly that motivation that caused me to still be perplexed by something that happened six years ago to then enroll people in a control trial to really understand if they were the people that were going to teach me a new thing. So I think we have tried to continue to penetrate to see is there something here we're missing. We've been devoted actually to that pursuit, I would say, and happily we're not being having to develop a new kind of broad basis for our understanding of olestra. These studies continue to fit into a kind of fundamental understanding.

CHAIRMAN BRANDT: Dr. Byers.

DR. BYERS: I just have a couple comments really, not a question. It seems to me that Procter & Gamble and CSPI and FDA agree that there are some GI effects, and certainly that's reflected on the current label, and that for most people who are going to experience those effects, those effects are small, certainly of the order of magnitude as we have with dairy products and beans and bran muffins

and so forth. So it seems to me that there is substantial amount of agreement on that.

Whether or not some people have a more immediate or more severe reaction, to me the rechallenge study is reassuring, that for most people who perceive that they have immediate severe reactions, in fact, it's not attributable to olestra. Whether or not there are, in fact, however, in the general population some numbers of people who, in fact, do have that, I think is a question that can only be answered by continued rechallenge studies. I think the one thing that has not been fully addressed in the analyses and probably in the study design so far has been this possibility of interactions between olestra and other kinds of foods. The episodic nature of some of the reactions within the 20 gram group, for instance, in the trial and so forth, I think, could be addressed better in the future, which really leads me to my final comment which is the interaction with food.

And I think as we look at this post-marketing active surveillance system this afternoon, and as we consider the effects of olestra that are well documented on the absorption of fat soluble nutrients from vegetables and fruits, I think it's the interaction with food that's going to have to have more attention in the future.

CHAIRMAN BRANDT: Dr. Fennema.

DR. FENNEMA: Yes. We've heard several anecdotal accounts about severe reaction to consumption to olestra, and I'm curious, and maybe this was said, but I don't recall it being said or discussed, in your controlled studies, either in the placebo groups or in the olestra groups, did you encounter incidences which were comparable to any of those anecdotal studies in terms of severity is what I'm talking about?

DR. ZORICH: Absolutely, yes. We have encountered particularly in the large population-based studies, if you recall, I presented some data on the number of people going to physicians and the number of people going to hospitals, and yes, these people are out there, and they were not different between the two treatment groups.

CHAIRMAN BRANDT: Dr. Benedict. No, Dr. Jacobson. I'm sorry. I didn't see your hand. You're going to respond to his question?

DR. JACOBSON: Yeah. I don't know if your question was limited to the most recent studies, but there are at least two earlier studies that demonstrated severe--

CHAIRMAN BRANDT: Let's not get back before 1996, folks.

DR. JACOBSON: --GI effects. Well, I think his question was do these ever appear, do severe effects ever occur in controlled studies?

CHAIRMAN BRANDT: Okay. Go ahead.

DR. JACOBSON: And there are at least two studies where severe effects occurred. One was in the eight week clinical trials, as the FDA explained in the Federal Register, where there was a statistically significant increase in severe symptoms in both the 20 gram per day group and the 32 gram per day group where 26 percent in the 20 gram per day group, 26 percent of the people experienced one or more severe symptoms as compared to five percent in the control group.

And then in the 32 gram per day group, 22 percent versus five percent in the controlled. So there didn't seem to be an increase, although the maximum days duration of the severe symptom increased as you go from zero up to--with zero grams it was maximum was one day, eight gram per day maximum was one day, 20 gram per day maximum was two days, 32 gram per day maximum was four days.

So those are the eight week studies. Also in the earlier consumer rechallenge study, where, remember where people were qualified twice to get in, they had to be people who reported they were sensitive, then were screened, and there were 16 people in this study, and the number of people reporting severe diarrhea in the control was zero. The number of people reporting severe diarrhea in the ten gram per day group, two out of 15 people reported severe

diarrhea, and six out of 16 people in the 20 gram per day group reported severe diarrhea. So it went from zero percent to 13 percent to 38 percent, which--and the 38 percent was statistically significant.

CHAIRMAN BRANDT: Okay. Dr. Benedict.

DR. BENEDICT: I was not sure I was going to raise this question, but the discussion seems to be grinding slowly to a halt.

CHAIRMAN BRANDT: And you refuse to let it.

DR. BENEDICT: I refuse to let it die. I am having such a wonderful time. I'm sensitive to Dr. Sandler's study about inherent frequencies of difficulties that people have, and I'm sensitive to Dr. Klontz over here with his recurrences at an irregular interval. And the question, and let me preface it by the fact that I have absolutely no biological basis for suggesting this, but have you or your consultants considered the unlikely possibility that, in fact, some people might be responsive to olestra, but that that first response--this is embarrassing to almost suggest--provides a desensitization wherein now when you rechallenge, of course, according to that weird hypothesis, they won't respond anymore, and so they might have a primary response but you won't get another one? And I don't even know why I'm asking this, but it's been bothering me for three years.

[Laughter.]

DR. TREIBWASSER: Well, I think the--I mean didn't the analysis Dr. Klontz talked about in the 20 gram group that shows his on-off recurrences, I mean, you know, some of these symptoms in some of these people who are eating the product constantly on a continuing basis come and go. But I think when you look at the rechallenge data, you know, you can see pretty clearly that if someone thinks they were sensitive or intolerant, you go and challenge them, they don't respond.

DR. BENEDICT: I think that's my point. I mean my spurious point is you rechallenge them, they don't respond, maybe they somehow desensitize themselves?

DR. ZORICH: Yeah. Well, they actually do respond, but they respond just as often as when they're eating full-fat chips. Their response rate is independent of what they were eating. They continue to respond. Every week 25 percent of them had something.

DR. BENEDICT: Ah.

CHAIRMAN BRANDT: Dr. Chassy.

DR. BENEDICT: I'll quit.

DR. CHASSY: I'm a little bothered by the semantics of this conversation. I don't know how to phrase this. We're comparing data from clinical studies where the subjects grade their reaction as moderate or severe, but

they continue in the study, they may not lose time, it may be a low impact but severe on that scale. The study is designed to look at a very different thing with these acute reactions that people may or may not be having when they call into an 800 number and report, and those are the people that are being channeled back into these rechallenge studies, and you're looking for a very different kind of reaction. It's an acute response to a single dose as opposed to whether someone alternates on and off.

I mean what you might find is they have pizza every Friday night and that taken with olestra is bad, but that's a different issue than these acute reactions we're hearing about.

DR. ZORICH: Yes. I thank you for pointing out that inconsistency. Back to the question--oh, this gentleman left--if we're asking about whether or not in 90, 91, 20, those old studies that were recent, just brought up again, if people went to the doctor, went to the emergency room, absolutely not. There was no indication. We're just using the semantics of a word to try to twist a point, I think, here. The point--I spoke with every one of those people in those studies and no one was having the kind of reports that we heard here today. There was nothing like that in those studies no matter how they graded it in the study. That's a completely separate topic from was there

anyone in those studies like what you heard today, and I can say to you absolutely not.

CHAIRMAN BRANDT: Okay. We are now at the end of our discussion period. It is now 11:40. We will break for lunch. We will reassemble--everybody be reassembled at 12:40 promptly, and Procter & Gamble will be prepared with all their folks.

[Whereupon, at 11:40 a.m., the meeting recessed, to reconvene at 12:40 p.m., this same day.]

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

[12:40 p.m.]

CHAIRMAN BRANDT: Okay, committee, get together here. Come on. You're getting paid big bucks. Let's get together here. Where is all the rest of our folks? Round them up. Audience, I'm not concerned about. The committee I'm concerned about. Okay. Let's go. Let's go. Let's go. Okay. Everybody on the committee, homework tonight. Okay. For all of you who were planning on partying, get to bed early and do your homework because tomorrow, I will be polling you individually--we don't vote--but individually each of you will have to address each of the three questions that were posed in our charge.

So think about what you heard up until now in a day and a half and what you're going to hear this afternoon and, of course, you can't think about what you're going to hear tomorrow morning yet, but you can think about what you've heard yesterday and today this evening, decide what it is you want to say, and you will be polled. For those of you that have early flights, please advise Dr. Larsen so I can get you early. By early flights, I'm talking about noon or before. So I will get your early on because we need your wisdom before you board an airplane.

Any questions about that from anybody? Everybody knows what the three questions are that you're going to be

asked to address. Again, I would remind you that in your study and in your ruminations about these issues, you ignore anything that occurred before January 1996. Okay. Well, you have to. That's the rules. I didn't make the rules. I just abide by them. So you got to forget about anything that occurred because that decision has been made. We're not here to rehash it, and I have a note that I can't read it. Oh, good. Okay. We do have two guest experts with us that need to identify themselves. Dr. Bernstein, just in the microphone, tell us who you are and where you're from.

DR. BERNSTEIN: I'm Dr. Paul Bernstein. I'm an ophthalmologist from the University of Utah, the Moran Eye Center, and I'm a half-time clinician, specializing in retina detachments and age related macular degeneration. I'm also a researcher, and my basic research is on carotenoids in the eye.

CHAIRMAN BRANDT: Okay. And Dr. Crouch.

DR. CROUCH: I'm Rosalie Crouch. I'm from the Medical University of South Carolina and my area is vitamin A metabolism, particularly in the retina and pigment epithelium.

CHAIRMAN BRANDT: Welcome to both of you. We're delighted to have you join us, even if it is for a short while. Your sentence is not long. But we're glad you're here. When we get to the questioning and comment period,

feel free to say anything you want as long as you don't it being recorded which it will be. Always use the microphone, as I've just recently been chastised to do, and everybody will be happy. Okay. Any questions, comments, further stuff? You got any administrative stuff? Okay. And we're ready to go. Proctor & Gamble is going to talk about further about their active surveillance data. You have 80 minutes and give me a minute to set the--all right. Well, isn't that amazing. Oh, do one hour and 20 minutes. Oh, okay.

[Laughter.]

CHAIRMAN BRANDT: Okay. One hour and 20 minutes. Go.

DR. PETERS: Thank you. Good afternoon. I'd like to first--

CHAIRMAN BRANDT: And let me just interrupt you one minute and say remind all of your colleagues they got to be wired and turned on.

DR. PETERS: Yes, sir.

CHAIRMAN BRANDT: Okay. Otherwise nothing they say counts.

DR. PETERS: Okay. Can I have seven extra seconds for that?

[Laughter.]

CHAIRMAN BRANDT: Yeah, you can have it.

DR. PETERS: I'd like to thank the committee for allowing us to present the new data we've collected since approval.

[Slide presentation.]

DR. PETERS: I must say looking at some of the familiar faces, I feel a bit like Bill Murray in that movie "Groundhog Day," where he keeps living the same day over and over again. But I will tell you that I hope as you'll see we've been really busy since we were here last to present our data, and we have a lot of new information to share. So with that as a brief introduction, let me tell you a little bit about what we'd like to cover in the next 80 minutes or so.

We're going to begin with a little bit of contextual background about what was known about the nutritional safety of olestra at the time of approval. Then we'll proceed with a series of presentations which review the data that have become available since 1996 in the area of carotenoid research, and since we don't have time to go through this in great detail, we've handed out the comprehensive review of this literature that we've done over the past several months.

And finally we'll talk about the work that was initiated at the time of approval to do population based studies to understand how people use olestra foods in their

everyday lives as part of their diet, and whether there are associations with that consumption and serum levels of fat soluble vitamins and carotenoids.

To give you a little bit more detail about the line-up, it is going to be tag-team here, but let me just tell you a little bit about who is going to speak. I'm going to provide a general review which hits some of the highlights of what's become available in this area in the last couple of years. Then Dr. Gil Omenn will talk about some specific expertise he has in recent intervention trials that have become available. Dr. Allen Ho will talk about recent developments in the area of age-related macular degeneration. And then we'll commence with the population based studies that the Fred Hutchinson Cancer Research Center have been conducting looking at how people use these foods in their diets and what associations there are with serum nutrient levels and finally we'll talk about a study that is hot off the press, which is really kind of a nifty study that Drs. Tom Ciulla and JoAnn Curran-Celentano have conducted. Dr. Ciulla will present the results from this new study which looks at the macular carotenoid pigments in the eye in association with lots of diet and lifestyle factors including olestra consumption for the past year in one of the main test markets.

Well, with that as background, I'd like to review

briefly what was known about the nutritional safety of olestra at the time of approval. Extensive studies looking at olestra consumption in animals and humans demonstrated that olestra does not affect water soluble vitamin or mineral absorption, nor does it interact with the major macronutrients in the diet, protein, carbohydrate or fat.

Now, because olestra is a non-absorbed lipid that passes through the GI tract, it can interact with other highly lipophilic molecules such as the fat soluble vitamins that are eaten at the same time. I just want to point out that this effect simply reduces the efficiency with which these compounds are absorbed from the diet. It doesn't abolish their absorption, nor does it pull vitamin that's already been absorbed by the body out of the body.

Finally, fat soluble vitamins are added to olestra products to compensate for this reduced absorption, any potential reduced absorption as specified in the Federal Register approval.

Now, at the same time that that information was available, FDA had done an assessment looking at whether or not carotenoid addition would be needed based on the currently available data. It concluded that at that point in time carotenoids have no identifiable health benefit except for the pro-vitamin A role of beta carotene. They base their assessment on looking at the comprehensive

literature which included an assessment recognizing that diets high in fruits and vegetables are associated with reduced disease risk, but there was no direct evidence that it was not the carotenoids in those diets rich in fruits and vegetables that were responsible for conferring protection.

And finally the randomized studies that were available at that time, which had looked specifically at carotenoids and disease prevention, had not shown any beneficial effects of carotenoids to reduce disease.

Now, at the same time FDA also added that the actual magnitude of olestra's effects on carotenoid absorption was likely to be within the range of normal meal-to-meal, day-to-day variation in the diet. For example, as Dr. Schwartz mentioned earlier this morning in the public comment period, carotenoid absorption from the diet is highly variable, influenced by a number of factors. If you were, for example, to eat a salad at lunch with a fat-free salad dressing, you get virtually none of the carotenoids from that salad compared to a situation where you would eat it with a full fat dressing.

Likewise, if you eat a carotenoid containing food with certain types of dietary fiber, that will diminish absorption of carotenoids substantially. So these are common dietary situations no different than if you were to consume an olestra snack with a carotenoid containing food,

as part of the range of differences that occur meal to meal.

Now, let me turn to what we've done since approval since that's what we're here to talk about today. First of all, we've really done two major areas of research. First, we've been looking at all of the literature that's come out since approval to stay on top of the carotenoid field because it continues to develop over time. And finally, we've initiated a series of large studies looking at population based monitoring of olestra use in the population, how do people use this, how do they use it in their diets, and is there an association with serum nutrient levels?

So several hundred papers have published since 1996, and I've provided you a summary of those in the book that we've handed out, which to our knowledge captures everything that was in the published peer review literature. There are about 217 references which we've reviewed, covering a wide range of different aspects of carotenoid research, and I'd like to provide some highlights now of what some of the area, some of what has been published in these areas, specifically the ones that have received a lot of attention.

First, I'd like to talk about the intervention trials because they provide the only direct evidence available in the scientific community of whether carotenoids

themselves might be protective. Then we'll talk a little bit about prostate cancer and age-related macular degeneration, which are two of the newer diseases where research has begun to explore potential relationships or associations with carotenoids and other diet and lifestyle factors.

And finally I'll talk a little bit about some alternative hypotheses that are beginning to emerge as research broadens for what it is about the lifestyle and the diet of people who eat lots of fruits and vegetables that might confer protection against chronic disease?

So there have been three large intervention trials that have been completed, and several other smaller ones. I've shown the three largest ones here. Two of these have published since the olestra approval, and all three of them had shown the same thing, that is that supplemental beta carotene did not prevent lung cancer or cardiovascular disease, and several other things have been looked at in follow-up analyses.

I just wanted to point out that the two that looked at high risk groups, that is people that are at high risk of lung cancer, smokers mainly, there was an actual increased risk of lung cancer and cardiovascular death in these trials, whereas the Physicians Health Study, which was in a lower risk population, showed no benefit nor

importantly did it show any detrimental effect either, and Dr. Ho or Dr. Omenn will mention more about these trials in a little bit.

Now in the wake of probably 15 or more years of looking at beta carotene, certainly other carotenoids have emerged on the landscape as of interest, and lycopene is one of them. An interest in lycopene and prostate cancer was stimulated by a study done by Dr. Edward Giovannucci at Harvard, and he published a study in which he found that there was a decreased risk of prostate cancer when individuals ate ten or more servings per week of tomatoes, tomato sauce and pizza or these other tomato containing products. And these authors concluded that possibly it was something in the tomatoes themselves, perhaps lypopene, which might be associated with that reduction in risk.

Now, since that initial finding was published, there have been several other studies that have looked at the same issue and have not been able to reproduce that finding at least to date. Key, et al. found no association with cooked or raw vegetables and tomatoes and lycopene specifically. The same is true in this study with lycopene, and then serum lycopene was looked at in the study by Nomura, and they did not find an association with reduced disease risk.

Now, to switch gears a little bit and talk about

one of the other new diseases on the block that's been looked at with relationship to carotenoids, certainly there has been a lot going on for years in this area, age-related macular degeneration and carotenoids really, I think, made it on to the radar screen with a very important study that Dr. Joanna Seddon at Harvard published in 1994, in which it was observed that high intakes of spinach or collard greens was associated with a reduced risk for developing AMD, age related macular degeneration.

And spinach and collard greens contain lutein/zeaxanthin and beta carotenes, some important carotenoids in the diet. Since then, however, other studies looking at the same kinds of relationships between diet or serum and AMD have not found the same relationship. The large Beaver Dam study by Mares-Perlman has found that carotenoids, and specifically they looked at lutein/zeaxanthin, as well, did not correlate with reduced disease risk, and finally Smith, et al., in a smaller study looked at serum beta carotene, which tends to track with the lutein and zeaxanthin, also did not associate with reduced disease risk.

But there have been a lot of other developments in the AMD area over the past several years. There's been a lot of work in understanding the role of genetics. Over 17 different susceptibility genes have been identified that may

predispose people to getting this disease. The concordance of AMD among relatives is quite dramatic, 100 percent concordance among identical twins, about 40 percent concordance among heterozygotic twins, and then finally a number of different diet and lifestyle factors are being studied for their potential role in predisposing individuals to getting this important disease. 35 separate factors have been identified that may be associated with risk. 16 of those are diet related, and include a wide variety of different factors such as saturated fat, flavonoids in things like wine and zinc among others.

Now, diet and disease is obviously very complicated interaction, and it's not a single factorial but a multifactorial relationship undoubtedly. So there have been a number of studies that have been done looking at other things that may be involved in the disease process. Other factors that may explain the protective effects seen with high fruit and vegetable intakes, among these are other factors in the plants themselves, namely phytochemicals. There are an estimated five to 10,000 of these in the diet. Many of them have been looked at. There are stronger anti-oxidants in many cases than the carotenoids, and they have other biological functions as well.

It's important to note that of the main categories that have been looked at, none of them are highly lipophilic

and so therefore they would very unlikely be involved in any interaction with olestra. Their lipophilicity indices are several-thousand fold less than even the fat-soluble vitamins.

Now, what about other lifestyle factors? I just wanted to mention a recent study that CDC did looking at people who eat five or more servings of fruits and vegetables a day, they looked at other behavior that tended to cluster with those healthy looking diets, and they found that these people that had these high fruit and vegetable intakes tended to be non-smokers, consume little alcohol, have higher levels of physical activity and pay greater attention to health monitoring such as monitoring their serum cholesterol frequently.

This just points out that it's very difficult to parse out the different contributions of both diet and lifestyle to chronic disease risk. So I think we need to keep in mind the breadth of different factors that may be involved in conferring protection from disease.

So, to summarize, and this was obviously a jet tour through the literature--that's why I provided the larger and comprehensive review--there really isn't a lot that's new on the landscape in terms of being able to conclude that carotenoids themselves are protective. There is new information. There is new associational data as well

as intervention trials to look at, but the data have not yet established that carotenoids themselves provide the health benefits, although research continues.

Now, I would like to introduce, just make one other little concluding remark here. This conclusion that we can't yet conclude that carotenoids are the protective factors is very consistent with recent dietary recommendations from a number of organizations including the International Agency for Research on Cancer, the American Cancer Society, and other organizations, who have continued to recommend increased consumption of fruit and vegetables as part of a healthy diet and lifestyle.

None of these organizations have concluded that it is the carotenoid component specifically that is responsible for decreased disease risk. I'll just point out the one caveat. The AICR report did say that for lung cancer, they thought it was probable that beta carotene specifically was protective for this disease, but we have other data from intervention trials that can help put some perspective on that.

And finally, I'll just summarize what the IARC, the International Agency for Research on Cancer, reported, which was that it concluded it should not be assumed that the protective effects of diets rich in fruits and vegetables and carotenoid containing food specifically are

due to any individual carotenoid.

With that, I will turn the microphone over to Dr. Gil Omenn who will say a little bit more about the intervention trials.

DR. OMENN: I'm delighted to have this opportunity to appear before such a distinguished committee. I recognize many of you, and I'm impressed that the FDA has gathered you for this important decision. I have distributed, I believe, a written copy of my testimony so that you may have the text as well as the figures. Has it been handed out? Please?

CHAIRMAN BRANDT: It's not handed out yet.

DR. LARSEN: It's not handed out yet because we didn't have quite enough copies. We're getting some more made and once that's made, we'll distribute it.

DR. OMENN: Thank you.

CHAIRMAN BRANDT: Up until then, we're going to listen to you.

DR. OMENN: [Slide presentation.] Well, as you've heard extensively this morning, I'm sure, dozens of observational studies have shown a statistical association that people who eat more fruits and vegetables and therefore more beta carotene, more carotenoids, more folic acid, and lots of other constituents of fruits and vegetables have lower incidence of epithelial cancers and of heart disease

than do people at the other extreme who generally eat few to none. Such an association, however, proves nothing about cause and effect. Remarkable advances in the field of epidemiology during the past two decades have been fueled by the emergence of two kinds of studies: laboratory investigations of biological plausibility and genetic, nutritional and other heterogeneity among the participants, and randomized clinical or prevention trials in appropriate human populations to test the hypotheses arising from observational studies.

It is astonishing to me that prominent scientists and consumer advocates would continue to assert that beta carotene is responsible for a quote "protective effect" based only on the statistical association. The heart of the biological hypothesis tied to antioxidant effects and especially quenching of singlet oxygen species has collapsed. Beta carotene turns out to be a weak to poor antioxidant. Furthermore, according to William Pryor of Louisiana State University and Norman Quinsky of Tufts, beta carotene is readily oxidized to hypoxides and other metabloids which Pryor has now found to be pro-oxidant and pro-mutagenic.

The attractive notion that beta carotene, which is physically present in low density lipoprotein particles in the circulation, would protect against LDL oxidation and

thereby reduce the risk of atherosclerosis was supported only by in vitro assays. Now, several major laboratories have reported that beta carotene fails to provide any such benefit in vivo. Even more troubling are the results from a portfolio of large-scale randomized chemo-prevention trials as Dr. Peters just summarized. These were initiated in the early 1980s by the National Cancer Institute to test whether beta carotene or combinations of beta carotene with vitamin E or with vitamin A would reduce lung cancer incidence, as had been predicted by Peto, et al.

In 1982, my colleagues and I at the Fred Hutchinson and the University of Washington were sufficiently impressed with the possibility that beta carotene and vitamin A together could be cancer chemo-preventive agents that we proposed the Beta Carotene and Retinol Efficacy Trial, CARET. There were several lines of evidence, as you see here. The design was a two-armed placebo controlled trial after a factorial pilot phase to determine that there were no detectible adverse effects.

As is commonly true--next--in big epidemiological studies and trials research, the main results of many years of work can be summarized in one side, and here it is. Many of you are familiar with this problem. CARET participants receiving the combination had no chemo-preventive benefit and had excess lung cancer incidence and mortality.

Furthermore, these results are highly consistent with those previously reported, which you had available to consider in 1995, but which were widely discounted by the scientific community and the media.

Next. Comparing the two studies, lung cancer incidence data shows separation of the rates for the two treatment arms after about 18 months and progressive sustained excesses of lung cancer in the active treatment arm, about six versus five per 1,000 persons per year. These results are so striking and were so consistent with the ATBC result that the Safety and Endpoints Monitoring Committee for CARET and the NCI recommended to us and my colleagues and I, who were the responsible steering committee investigators, voted to terminate the active intervention in CARET on January 11, 1996, Dr. Brandt, immediately following the date that you indicated for the beginning of active consideration of new studies today.

That was 21 months ahead of schedule in order to protect the participants from further exposure. These results also led to the removal of beta carotene from the 40,000 woman study at Harvard, the Women's Health Study, though not after a lot of back and forth from their much smaller study, the Women's Antioxidant Cardiovascular Study.

The CARET participants are no different from all

the other populations that have been studied. Their baseline inverse correlation with the disease risk is the same. But all subgroups of CARET had excess relative risks except for former smokers, whose point estimate was 0.8, but whose 95 percent confidence interval in that estimate overlapped the total population, and surely you all are aware of the problems of subgroup analysis and overlapping confidence intervals. I'll come back to this in a second.

Next. Mortality rates moreover were similarly adverse in both trials. Cardiovascular mortality--next--was increased in the active arm as shown here for CARET. All subgroups--next--had a relative risk greater than one and shockingly here even the former smokers had a substantially increased risk which vitiated our consideration of continuing the trial in the former smokers only in the hopes that we might be able to reinforce smoking cessation and protect former smokers.

This is consistent--next--with results from ATBC published since 1996, both for angina pectoris shown here, increased risk with beta carotene, statistically significant. And--next--for fatal coronary heart events in the bottom frame, 1.43 relative risk for beta carotene in fatal coronary heart disease in the smokers in Finland.

Next. The lung cancer incidence and total mortality results are plotted for ATBC, CARET, the

Physicians Health Study, which also came out in January 1996, and the Linxian populations trials which were totally different population. You can see the big trials with the large circles are clearly adverse.

Finally, I present some of the media coverage. This may be amusing to you or a good lesson about expectations and lack of acceptance of scientific results. The main newspapers and magazines had a hard time accepting the ATBC results. If you look from the bottom up--lift it from the bottom, please--"Beta No More--Doesn't Work," Time magazine; "Ineffective," Wall Street Journal; "Not Preventive," International Herald Tribune. "A Dud," New York Times. But the small city papers got it straight back in 1994.

In Abilene, Texas, "Completely Unexpected, Major Study Suggests Beta Carotene Causes Cancer." Seattle Times, "Beta Carotene May Cause, Not Prevent." The New England Journal editorial that went with the 1994 article which was all you had to review from intervention trials a couple of years ago, written by Hennekens, Buring, and Peto said "Benefits Not Yet Proved." Well, now you've got more evidence. We all have more evidence. The cereal manufacturers have removed beta carotene from their cereals. Most of the supp manufacturers have done the same, and we are trying to protect the public from a carcinogenic risk or

at least surely from no benefit.

In the best sense, these unexpected scientific findings have stimulated a new generation of laboratory studies and clinical studies about the actions of beta carotene and other carotenoids and a broad search for other reasons why people who eat a lot of fruits and vegetables are at lower risk than people who eat less. The FDA, and this advisory committee, I respectfully submit, should reiterate the judgment rendered in early 1996 that carotenoids have no demonstrated health benefit role in humans except for the important pro-vitamin A role of beta carotene.

Further, I hope that you will reinforce the principle that epidemiological associations should be put to the test and the trials trump associations. Thank you very much.

CHAIRMAN BRANDT: Thank you, sir.

DR. HO: Is this on?

CHAIRMAN BRANDT: Yes.

DR. HO: Okay. Dr. Brandt, members of the committee, I appreciate the opportunity today to switch gears a little bit and provide you with an overview of age related macular degeneration, the number one cause of blindness in this country for individuals over the age of 50.

[Slide presentation.]

DR. HO: I'm a retina surgeon at the University of Pennsylvania, and also direct a reading center on prevention of AMD in this country and an international study group looking at palliative therapies for late forms of this disease. First some basics. The eye can be likened to a camera, and what we're talking about is the retina, which is the seeing part of the eye, like the film in the camera. It's in the back of the eye. The retina is the same part of the eye that harbors vision cells and as light is focused on the retina through the lens which can become cloudy with time and become a cataract.

Why macular degeneration? Well, it's macular degeneration because the macula, that part of the retina that subserves central vision, the ability to read, drive a car, see someone's facial expression, is the focus point of the eye and occurs right here adjacent to the optic nerve. The optic nerve is the cable that leads from the eye to the brain. Here's an example of a patient who's 35 years old with the normal healthy macula. The visual acuity is 20/20. Here's the 65 year old gentleman enrolled in one of our trials who has dry, age related macular degeneration, and the hallmark of this disease are these little yellow spots called drusen. These drusen do not necessarily cause vision loss.

There are two forms of the disease, the dry form and the wet form. The dry form is completely compatible with good vision. This patient has 20/20 vision. The wet form characterized by bleeding, scarring, leakage, in the macula is associated with vision loss. Now no one understands why these drusen or age spots occur in the macula, and this is a cross-section. This is the retina right here, and these little lumpy, bumpy expressances that are pink here represent the drusen that are beneath the macula. This is also associated with a thickening of the basement membrane and there is no good animal model for this disease.

When loss of vision occurs, blood vessels invade these areas of drusen, grow beneath the macula, that part of the retina that subserves central vision, and they bleed and leak and scar, and that's how you lose central vision. Here's an example of what it's like from the patient's perspective to lose vision from this disease. You lose central vision but not your peripheral vision. As you can see, it's disconcerting. That patient would not be able to read a book, newsprint, and would not be able to drive a car.

This is a significant disease. And the prevalence is significant and individuals over the age of 60, 30 percent of people have age-related macular degeneration in

this country. It's the number one cause of blindness among elderly Americans, as I said before, and to give you some perspective on the impact of the disease, you can see that in 1998, approximately 200,000 people per year will go blind. Compare this to the stroke rate annualized in the USA which is about 6,000 events.

By the year 2030, with the aging of the population, we expect approximately 500,000 people per year to go blind from AMD. Now, the mechanisms of this disease are not well understood. Paul Bernstein, for example, is starting to explore some of the biochemical and cellular mechanisms of AMD, but the real mechanisms are not known. However, there is an evolving literature on associated risk factors for macular degeneration. I've divided these into modifiable risk factors and those that are not modifiable, and if you look at the modifiable risk factors, the most compelling risk factor is smoking, and in multiple studies, in multiple population groups, there is a very, very strong dose response relationship between smoking and more severe forms of AMD.

There's a hypothesis that cardiovascular disease and risk factors associated play a role in AMD. This has not been borne out and there are conflicting results. There is a hypothesis that anti-oxidants, carotenoids, may play a role in AMD, but this has not yet been borne out. There's a

hypothesis that light exposure is involved in this disease, but that has not been borne out. There are conflicting results again.

Well, what are the other non-modifiable risk factors? The strongest risk factor for this disease is age, and an octogenarian is much more likely to have macular degeneration than someone who is 50 years old, for example. Race is also a very strong associated factor, and Caucasians are much, much more likely than African Americans, for example, to have AMD. A family history and a familial predilection for this disease speaks to a likely genetic component although it's likely polygenic and very complicated.

Treatments for this disease today are unfortunately very poor. Our only proven treatment is laser therapy, and if you look at the average visual result after five years after laser treatment, that is legal blindness, 20/200 vision. So we need to do better for this disease.

In summary, macular degeneration is a significant disease and the number one cause of blindness among elderly Americans. The mechanisms for this disease are being explored now, but our understanding is definitely incomplete. Risk factors are we're starting to develop a profile, but this literature has really just come about since the mid-1980s. We, and many other people around the

world are working on new therapies and a better understanding of what causes this condition. Thank you.

DR. PETERS: Thank you, Dr. Ho. Could I have the next slide, please?

[Slide presentation.]

DR. PETERS: What I'd like to do now is turn to what you probably all have been waiting for, which is what have we actually done to go out in the population and see what people are doing with olestra snacks and what have we been able to measure in terms of associations with either serum nutrients or as I mentioned, we have a study now that looks at the macular pigments in the eye. So I would like to now introduce Dr. Ruth Patterson from The Fred Hutchinson Cancer Research Center who will describe, begin describing some of this work.

DR. PATTERSON: [Slide presentation.] Okay. Today my colleagues and I will be presenting data from the first year of the olestra post-marketing surveillance study. this study was motivated by feeding trials which indicated that in highly controlled conditions regular daily intake of olestra was associated with reduced serum concentrations of some fat soluble vitamins and carotenoids. Therefore, our objective is to study olestra in the real world.

Specifically, to assess the consumption of olestra-containing savory snacks and to assess associations

of olestra consumption with serum concentrations. Briefly, I'll be presenting an overview of our study design and the specific aims and our operational organization. My colleague Dr. Kristal will present information on assessment of key variables and some descriptive findings, and finally Dr. Thornquist will present the multi-varied analyses, our conclusions and plans for future analyses.

In January of 1996, as part of FDA approval, Procter & Gamble agreed to conduct active post-marketing surveillance. In March, they assembled a team of expert scientists to advise them about the optimal design of such a study, and in June, the coordinating center was established at Fred Hutchinson Cancer Research Center, where we finalized the protocol and developed the procedures.

September, a clinical site was opened in Indianapolis, the first major test market, and in March of '97, three additional clinical sites joined the study. As I said previously, Indianapolis was the first major test market. This map shows you Marion County which is an area from which we created our participants. This slide is probably the most important slide I'm going to show you today because it illustrates the design of the study which is a repeat cross-section and cohort design.

The Olestra Post-Marketing Surveillance Study is best thought of as three-related studies, each of which

corresponds to one of our specific aims. The first study is a population cross-section study, which is a random digit dial telephone survey from which we obtained information about olestra consumption and co-consumption with fruits and vegetables and carotenoids. The second study is a clinic cross-sectional study which is composed of volunteers from the population cross-section. Participants visit our clinical site, provide us with detailed data on diet and other factors and a blood sample.

And from that we can assess associations of olestra consumption in serum nutrient concentrations. And the final study is the cohort. The cohort is selected from the clinic cross-section to oversample olestra consumers based on information from follow-up telephone calls. And this allows us to assess changes in serum nutrient levels. For each of these studies, we have data both before and after the introduction of olestra. Before I leave this slide, I'd like to make three additional points.

One, participants are not aware this is a study of olestra in order to minimize selection bias and recall bias. Two, participants are similar, very similar to the community from which they're drawn, because our eligibility criteria are minimal. You need only be greater than the age of five, able and willing to provide a blood sample, and not have any major medical condition which would dramatically influence

serum nutrient levels such as being on hemodialysis, for instance. And thirdly, participants upon completion of the clinic visits were paid $100 partly as an incentive but also just to reimburse them for their time.

This amount is similar paid to participants in the National Health and Nutrition Examination Survey popularly called NHANES. Okay. Specific aim one is to monitor the consumption of olestra containing savory snacks. We addressed this specific aim using data from the population cross-section, which is the telephone random digit dial survey.

Specific aim two is to assess the association of olestra consumption with serum fat-soluble vitamins and carotenoids, and we addressed this with data from the clinic cross-section, which is composed of two separate samples, one drawn before the introduction of olestra in the market and the second one drawn after the introduction approximately a year later.

And the third and final specific aim is to assess the association of olestra consumption with changes in serum nutrient levels, which we address using data from the cohort, which is a group of people from whom we obtained a blood sample before the introduction of olestra and afterwards, approximately one year later. So we can calculate the difference.

I'm going to switch tacts briefly and talk about our organization. The steering committee controls all the science of the study. All publications and presentations must be approved by the steering committee, which is composed of study investigators. The data and the sera reside at the coordinating center, and the data that you will see presented here today were delivered directly from the Fred Hutchinson Cancer Research Center to the FDA. The advisory council continues to meet regularly with study investigators to review study progress and the FDA has been an observer at most of these meetings.

As I mentioned previously, the steering committee is composed of the project investigators including the three scientists at the coordinating center and invest the principal investigators at each of our clinical sites in San Diego, Baltimore, Minneapolis and Indianapolis. Westat is a research contract firm which manages the site in the Indianapolis for us and conducts our telephone based recruitment. The Olestra Surveillance Advisory Council is chaired by Dr. Gil Ommen and each of the scientists on the advisory council brings expertise in particular areas that are important to our endeavor.

Operationally, again, the steering committee makes all decisions about our procedures and the protocol. Coordinating Center works closely with all the clinical

sites to assure consistency and quality control, and the sera are analyzed at Tufts for vitamin K and quintiles for other anolytes. This slide shows the study center sites. The three additional sites were chosen based on two criteria. One, access to diverse populations. In particular, Baltimore has a large black population. San Diego has a large hispanic population, and the expertise of our principal investigators. Dr. Cheskin at Johns Hopkins is a gastroenterologist and director of a weight management clinic. Dr. Cheryl Rock at UCSD is a carotenoid expert and Dr. Newark Steiner at the University of Minneapolis, Minnesota conducts nutrition related research in children and adolescents.

Finally, we note that the three additional sites successfully completed the baseline recruitment prior to the introduction of olestra in their respective markets and we will be continuing to draw the clinic cross-sections and following our cohort participants until the year 2001. Thanks and I'm going to turn over the podium to Dr. Kristal.

CHAIRMAN BRANDT: You all would probably do better to use the podium rather than keep--

DR. KRISTAL: Yeah. I think I'll do that. Thank you. Good afternoon. That's my name. That's my game. Okay.

[Slide presentation.]

DR. KRISTAL: I'll focus my description of methods on dietary assessment because our key independent variables are all based on dietary self-report. Now the key dietary measures in the study are olestra consumption, fruit and vegetable consumption, and intake of fat-soluble vitamins and carotenoids. And, in general, we use state-of-the-art methods when they're available, but as I'll describe, we also had to develop and validate some new measures for this study. We measured olestra intake by asking a set of detailed questions about consumption of savory snacks.

For the telephone-based survey, which we tried to keep under 12 minutes, we asked a set of structured items about the usual frequency of eating each category of snack, and by category I mean potato chip, tortilla chip and the like. If someone ate a particular category, then we probed for details on how frequently they ate each type, and by that I mean regular fat, low fat, non-fat or containing olestra.

In the clinic, we use an addendum to a complete food frequency questionnaire that asked about the frequency and serving size of consuming 19 different snack foods. We measured fruits and vegetables following the model on the telephone of the national five-a-day for better health evaluation, and in the clinic we used items from our food frequency questionnaire. And lastly, we measured nutrient

intake in a variety of ways. By telephone, we developed a modification of a standard 24 hour dietary recall, which we called a focused recall, and what this does is it captures quantitative information about the consumption of fruits, vegetables and savory snacks, specific to times during the day.

And we validated this instrument in a special substudy of 500 participants. Dr. Patterson presented that at the last International Dietary Assessment Conference and will be publishing those results. In the clinic, we used a food frequency questionnaire we developed for the Women's Health Initiative. Participants were mailed these food frequencies before they came to the clinic. They completed them at home and they brought them into the clinic where they were reviewed by a trained staff member. And we've also completed validation study on this food frequency and that has been submitted for publication.

The nutrient databases are these three. We use the University of Minnesota Nutrition Corning Center database for most nutrients. This is considered the best and most complete database in the United States. To this we added the USDA National Cancer Institute special carotenoid data. These are analytic data on fruits and vegetables on specific carotenoid content of foods. And lastly, we have the provisional analytic tables from Tufts University on the

vitamin K content of foods.

Now one unique aspect of the study is that we had to measure the consumption of carotenoids at the same time as people were eating olestra. This is because we know from earlier research that any effect of olestra absorption--excuse me--any effect of olestra on carotenoid absorption requires them to be eaten at the same time. So on the telephone, we had a set of structured items and we specifically designed the focused recall so we could get at co-consumption quantitatively of fruits and vegetables with olestra containing foods.

And in the clinic we used 24 hour recall. I want to point out that we developed extensive software programs to allow us to calculate from the focused recall and the 24 hour recall the percent of carotenoids that were consumed within a specific time period of eating an olestra snack. So, for example, we could tell you the percent of carotenoids that were consumed within an hour one way or the other eating olestra snack.

So, in summary, we used these state-of-the-art methods, but we also developed a set of new methods, and these were really required so we could validly address our specific hypotheses. Now, moving to our dependent variables, the HPLC run for carotenoids, vitamin E and vitamin A were done at Quintiles Laboratory, and I just want

to point out the coefficient of variation--this is from duplicate quality control samples--are all below ten percent, which is very, actually excellent for carotenoids.

We also used Quintiles to do our vitamin D and serum lipids. Again, coefficients of variations are quite low. And we used Tufts University to do the vitamin K and again coefficients of variation are quite low. So we did a very good job with the dependent variables.

So now I'd like to move to give you some descriptive results of our findings from--I'll start with the population cross section which again is the random digit dial telephone survey. So one of the first things you need to look at when you look at a telephone survey is consider the response rates. High response rate means that you can consider your sample to be a reasonably unbiased representation of an underlying population. So in this survey, we calculated efficacy rates, which were about 64 percent at baseline and about 61 percent at year one.

Now, efficacy rates are not interview rates and they're not response rates. These are better representation of the actual proportion of the population you manage to enroll. And the reason for this is that it includes a percentage, it includes everybody who refused the survey, including just hung up the phone when you called them, and it includes a portion of people who didn't answer or just

had answering machines in your denominator. So it's a more realistic representation of who you got.

And just for comparison, these rates are as good or better as one sees in other health surveys. Another thing to think about in RDD surveys is how well did you get responses from people who are generally hard to recruit to these studies, and in particular minorities, young people, and people not well educated. So in this study, we had about 60 percent women, and this is quite common because women most often answer the phone and are willing to cooperate, so this is just one of the things you get.

We got good representation to people in the younger age groups. We got about 19 percent blacks, and we got almost 45 percent of the people with high school education or less. So I think our survey techniques were successful in generating a reasonably diverse and generalizable sample.

Now one more thought before I show you actual results. It's important to talk about our model for understanding how people add new foods to their diet. And this is work we've been doing at Fred Hutch for many years, and it's basically on an anthropologic model called "diet individuation," and what this allows you to do is evaluate the potential dietary impact of adding a new food to the food supply.

So if you apply this concept of diet individuation to olestra containing foods, there is really three things people could do. They could substitute olestra snacks for other full-fat snacks, and in essence lower their fat intake. They could substitute olestra snacks for other low-fat snacks and essentially have no impact on their fat intake or they could replace other kinds of foods used for snacks with olestra snacks. For example, they could replace their fruit snack with an olestra snack or they could replace a candy bar, for example, with an olestra snack. And the last thing they could do is simply eat more, and I just want to say that in our culture this doesn't happen very much. We already are kind of saturated with eating. So if you're going to eat something new, you have to eat less of something else.

So this shows--I'll walk you through the slide here--this shows the percent of people in Marion County--and this is now population adjusted so it's representative of the population--who ate at least one serving of fruits and vegetables a day at baseline and at the year one follow-up. And for savory snacks, it shows the percent of people who ate savory snacks at least once per month in the previous month and again baseline year one.

What you see here is there is really no change between base line and year one in fruit and vegetables, the

portion of people eating at least one serving of fruits and vegetables. There is no change in the total savory snack consumption. Almost everybody eats at least one savory snack. Interestingly, at baseline, more people eat low and non-fat snacks than regular fat snacks. And now getting to year one, 15 percent of the year one sample--excuse me--15 percent of people in Marion County ate at least one olestra snack in the previous month. And I just want to point out that the suggestion here is that the consumption of low and non-fat snacks dropped somewhat, and I think what's happening here is that people are using olestra snacks again to substitute for low and non-fat snacks. There is no evidence anything is going on with regular snacks.

Just to emphasize that point. This shows the median and 90th percentiles of servings per day of fruits and vegetables and frequency per month of eating savory snacks, baseline, year one. There is absolutely no change in fruit and vegetable consumption. There is no change in total savory snack consumption, slight drop in regular fat, but a 14 percent drop in the median consumption of low and non-fat snacks, and olestra snacks, the median consumption among people eating them was three times per month.

We also looked at the demographic characteristics of olestra consumption by demographic characteristics, and what this slide shows is the percent of people eating

olestra snacks, their mean frequency of eating olestra snacks and the 90th percentile of consumption. What I want to point out here is that there is really not any difference by sex. There's a slightly decreased consumption among blacks and this was not statistically significant.

The only significant finding we have is that olestra snacks are consumed less often by people who are 55 years of age and older. So, as a summary, about 15.5 percent of adults ate olestra snacks at least once a month, and the take home is I believe people substituted olestra snacks for other low and non-fat snacks.

Now I'd like to move to the clinic cross-section. These are participants who are recruited from the telephone survey and who came into the clinic. The demographic characteristics I'll just briefly show you. They are about like the telephone surveys, 60 percent women, about 35 percent of people under age 35, about--somewhere between 19 and 21 percent black, and again about 40 percent of people with high school educations or less. Interestingly, only about half of these people were normal weight. 25 percent were obese and another 25 percent were overweight. And I think this is characteristic of our population unfortunately. About 30 percent smoked which is also what one sees in the general population.

This is what olestra consumption looked like in

our clinic sample. 217 people ate any olestra at all. That's 23 percent of the sample. And the frequency per month, .9 times, 1.2 servings per month, that's two ounce servings, and 8.1 grams per month. When we analyzed the association of olestra consumption with other variables, we categorized olestra into these groups you see here. Obviously, the nuns. There was a kind of a natural cut point around the 60th percentile. We looked for one at about the 50th but it didn't really make any sense. So about .4 grams per day and less was our low group. Up to the 90th percentile or .4 to 2 grams a day was our medium group, and then we had consumption at the 90th percentile was two grams or more a day.

And this shows associations of olestra consumption with some diet and diet-related factors. And there are really two important results here. One is that percent energy from fat decreased from 33.8 percent to 30.2 percent as people move from no olestra consumption to high olestra consumption. No association with the fruit and vegetable intake. None with BMI, and there is again a statistically significant decrease in cholesterol associated with olestra consumption from 187 to 178.

I want to move now to the cohort results. I won't show you demographic characteristics since they almost match those of the clinic. Olestra consumption was slightly

higher in this group because we selected them to be olestra consumers. It's 139 out of the 402 or so. That's 35 percent consumed any olestra snacks, and the frequency of eating it once a month, 1.6 servings, and 11.9 grams is a bit higher than in a cross-section. And these are the associations of olestra consumption. Now with change--because we had baseline and follow-ups, we're now looking at changes in diet and diet-related factor, and you can see there is a significant trend for change to reduce percent energy from fat from virtually nothing to negative 3.7 percentage points with high olestra consumption. No association of fruits and vegetables.

Unfortunately, this is a little noisy, but it's interesting that there is a slight decrease in BMI among the medium and heavy consumers of olestra. And there is this trend for serum cholesterol, which looks striking but is not statistically significant because of our sample size. So in summary, just to summarize those last two results, I think what we're seeing is that people who have decided to make significant dietary changes have also decided to use olestra.

So now I'd like to turn the podium over to Dr. Thornquist, who will describe the associations of olestra with serum concentration.

DR. THORNQUIST: Good afternoon.

CHAIRMAN BRANDT: Use the microphone.

DR. THORNQUIST: Is it on?

CHAIRMAN BRANDT: It's on.

DR. THORNQUIST: Okay. I'm sorry. Good afternoon. I'm Mark Thornquist, and I'll be talking about the results that we have in terms of association between olestra and serum levels of carotenoids and fat-soluble vitamins.

[Slide presentation.]

DR. THORNQUIST: One thing I should say keep in mind this is an observational study. All we can assess here are associations. We can't assess cause and effects. Now, on the other hand, typical statistical jargon is to talk about effects, and so I might use the word effect when I'm talking here, but keep in mind, all I can really talk about are associations. I think I'll pretty much skip this slide. I don't need to preach to the choir here on why one goes about fitting statistical models to analyze data when you have such a very highly heterogeneous population such as we have here. We're trying to reduce the amount of variability to get a more precise estimate of how parameters and to avoid possible confounding of our parameters with other covariates that we know are associated with serum levels.

Now we've looked at several different options for the way in which you would incorporate olestra into the

model. I mean we considered looking at, for example, grams of olestra per day, and decided not to use that method because to do so would have required us to make an assumption about the statistical form of the association between olestra and serum levels. For example, a linear association or a quadratic or something like that. We didn't want to do that. So instead what we did was to categorize olestra consumption into the four categories that we showed you to avoid having to make that assumption.

We're showing, by the way, this highest category, the 90th percentile, because we know that in the past the FDA has been interested in the people who eat olestra the most frequently, the top ten percentile among consumers.

Let me start off by talking about our results for the clinic cross-section. Once again, this is two independent cross-sections prior to olestra and post-olestra. And we discussed the modeling strategy we used here. What we did was we fit a model to our baseline data and then once we had our best fitting model to that, fit that same model to our year one data where we had olestra and added olestra into the model at that point. The purpose of doing this was to build a model on a data set that could not include any possible confounding of an olestra association. And then to fit the same model to a set of data that does have olestra in it and see what happens with

olestra when we put it into the model.

In fitting this model, we had two types of variables that we included. The first are what we call control variables. These are the standard demographics, age, sex and race, and two dietary variables: total nutrient intake from diet and supplements and total caloric intake. These variables were included in every model that we considered regardless of statistical significance.

We had a second set of variables that were included in models only if they were statistically significant. These variables include serum lipid concentrations, various other measures of dietary or supplement intake, and other measures of health behaviors or health status. Now we included these variables, we considered these variables for inclusion only if there was evidence in the literature of an association of those variables with the serum levels and biological plausibility for an independent effect of that rather than an effect mediated by some other variable that we were including.

A reason for doing this was to avoid potentially spurious associations that would result in additional variables being put in the model that weren't needed, basically to reduce the frequency of type one errors in selecting variables to include in the model. Well, what did we find?

Let's start off by looking at total serum carotenoids. This was our primary outcome measure when we went into this study. It was primary for two reasons. First of all, the total serum carotenoids include the most highly lipophilic of the compounds that we're studying in this study, and secondly, of course, olestra is not supplemented with carotenoids, and so if there is a true olestra effect somewhere, it would be most likely to be seen in this set of data. But, of course, we looked at all of our serum levels.

What are we seeing here? What we have here are the mean serum levels. These are controlled for covariates that we found to be associated with serum levels and they are weighted to be represented of the Marion County population. Here are the serum levels. Around them we have 95 percent confidence intervals, the error bars, and what you see is that these serum levels are basically distributed randomly. Well, as a statistician, I really shouldn't say randomly. But they're sort of randomly distributed.

[Laughter.]

DR. THORNQUIST: Around the mean level that we see in non-consumers. The amount of variability, there is no evidence of a trend, and it's all within these error bars. So, you know, just clearly looking at this, you're not surprised by the results of the bottom. The test for

heterogeneity, whether or not they're different, and the test for trend, whether or not there's a linear association, both have p-values greater than .8.

One last thing I'd like to point out on this slide is that we also include on here the number of individuals included in each of these subgroups. The more individuals you have in the subgroup, the more precisely we can estimate the mean for that subgroup, and therefore the smaller the error bar. And so these sample sizes found here explain the variation in the size of the error bars that you can see in these plots.

All right. So our take home message from the total serum carotenoids in the cross-section is there's no evidence there, no suggestion there of an association at this point.

Here are our results for the four fat-soluble vitamins, vitamins A and D, E and K. A couple of things I'd like to point out on here. For vitamin K, there was a statistically significant test for trend with a p-value of .03. The parameter estimate for that trend was roughly a ten percent increase in serum vitamin K per category from none to low to medium to high intake.

For alpha-tocopherol, the p-value for that, for the test of heterogeneity, are those four levels the same, was .08. There was this anomalously high level among the high

consumers, but a pattern that we don't anticipate is a real pattern. For vitamin A and for vitamin D, there is no evidence of any association going on. This slide shows again total carotenoids and three of its component carotenoids, alpha-carotene, beta carotene and lutein.

We include these three carotenoids in the same slide because the carotenoid levels in the serum are typically highly correlated because they're often found in the same foods, and so you'll see that people who tend to be high on alpha-carotene are also high in beta carotene and lutein. What you see again is no evidence of variation. Everything is within the sizes of these confidence intervals around here. No statistical evidence for a trend going on here. Basically we can find no statistical evidence in this of an effect at this time.

Here are the results for the other three carotenoids that we analyzed: lycopene, zeaxanthin and beta cryptoxanthin, and again you can see no statistical evidence there. The statistics are all in the report that we sent to you suggesting a trend in these data. So in conclusion from the cross-section, we did see statistical evidence of a trend for vitamin K with higher levels of vitamin K in people who ate more olestra. No other statistically significant evidence of trend or associations in any of the other analyses that we performed on these data.

Now, let me discuss the cohort, the people we brought back so we could analyze change. And we analyzed change in a very similar way. We basically fit a model to the change variable without including olestra, and then added olestra to that model. The control variables were the same as the control variables that we considered for the cross-section with the addition of the baseline serum level of that anolyte that we were looking at, and the additional variables were the same set of additional variables. In addition, we also allowed changes in those variables to be predictors in these models. We did not constrain the models here to be the same models as the ones that we fit for the cross-section because there could be different factors that predict change of serum level as opposed to absolute value of serum level.

Here are our results for total carotenoids. For change in total carotenoids now, between baseline and year one, the axis here now is percent change in carotenoids. Negative changes means that the serum level is lower year one compared to year zero; positive indicates that it's higher year one compared to year zero. And what we see is the serum levels bouncing around, no evidence of a trend in these, and no statistical evidence of an association in total serum carotenoid, in change in total serum carotenoids from this year one data.

Here are vitamins A, D, E and K, and we have a couple of interesting patterns here. For vitamin K, the test for trend had a p-value of .056. It didn't quite reach the .05 level. The point estimate for the slope was roughly ten percent per category, similar to the level that we saw in the cross-section, suggesting that this may, in fact, be a real effect. It's confirmed in independent data set.

The other interesting pattern was for vitamin D. Now it's not the pattern of serum level by olestra intake. I mean there's no pattern there. It's perfectly flat. What is interesting was that the serum levels were consistently 20 percent lower year one that in year zero. Now serum vitamin D, of course, is strongly affected by sunlight exposure, and the Midwest Climate Control Center reported that the average sunlight exposure in Indianapolis last summer and fall, prior to our follow-up period, was 25 percent less than the corresponding period a year previously when we had our baseline period, and we believe that this effect is simply due to less sunlight in Indianapolis last year.

Here are our data for alpha-carotene, changes in alpha-carotene, beta-carotene and lutein. Again, we see these things bouncing around, no suggestion of a trend. The test for heterogeneity here had a p-value of .052. The suggestion was that this medium intake level mean was

somewhat higher than the others, but again, no biological reason to think that that might be a true effect.

And finally, we looked at lycopene, zeaxanthin and beta-cryptoxanthin, and again we see nothing that is strongly suggestive of an association going on in these data at this time. So in summary from the cross-section of the cohort, we do see somewhat consistent data for vitamin K, the higher the level of intake, the higher the serum level, and the percent higher has the same estimate basically. No other statistically significant evidence, consistent evidence across cross-section and cohort, or evidences of trend that are suggestive of an association going on at this time.

Now let me make a comment that I would make in trying to interpret any null study. A null study is one that does not show an association. The conclusion you can draw from that is, of course, not that there is no association because no study can make that conclusion. All you can conclude is that associations beyond a certain level are unlikely. And this slide shows what level is unlikely to be truly out there and have our studies still show null association at this time. These are the effects that would have been detectible with 80 percent power using the test for trends that I've shown you in these previous slides.

For example, for vitamin A or for vitamin E, if

there had been a true trend between non-consumers to heavy consumers, where the heaviest consumers had ten to 12 percent higher or lower serum levels than non-consumers, we would have detected that trend statistically significantly 80 percent of the time in our data. The fact that we did not suggests that the trend is not likely to be of that size or larger. If there are true associations going on, they're smaller than that.

For total carotenoid, the trends that we could have detected with the test we presented so far are 16 percent changes between non-use and heavy use. And then we have obviously much higher trends detectable for the other fat-soluble vitamins and the individual carotenoids.

Now let me put this 16 percent, for example, explain that another way. Because there has been some discussion in the newspapers about a possible effect of olestra on serum carotenoids of ten percent or more. Now this is ten percent at the population level, and this is 16 percent non-users to heavy users. If we look at what this 16 percent corresponds to on a population level, while 23 percent of our participants, 23 percent of the people in Indianapolis we've estimated are eating olestra. So 77 percent would have no change in serum levels.

Of the 23 percent who are eating olestra, 60 percent would fall in our lowest use category, and they

would have one-third of this 16 percent difference, 5-1/3 percent. 30 percent would fall in the middle use category, and they would have two-thirds of that. So they would have about 10-2/3, and only ten percent of this 23 percent would have this full 16 percent effect. If you work out what that corresponds to, that corresponds to an overall population level effect of less than two percent.

So the suggestions that this could have an effect of ten percent or more on serum levels is not consistent with our data at this time. In fact, it's strongly inconsistent with our data. In general, if you want to get population level estimates, you'd have to divide these points here by nine. Now, this study is ongoing. We have a single site and a single year follow-up reporting here. When we're done in 2001, we will have four sites with three years of follow-up, and this slide shows the percent effects that are detectable at that time. Again, this is between, the slope between non-uses and heavy users. And you can see that for the cohort, we can detect ten percent or less effects, which would correspond to one percent or less effect in terms of population level means. And basically 15 percent or less for everything except alpha-carotene in the cross-section.

Now, the data for this analysis was available only by mid-March of this year. So we have not had time to do

all the analyses we intended to do, and which we will be doing on these data. Two of the analyses that we will be doing, have not had an opportunity to complete yet, include looking at serum levels in minors and looking at reports of GI problems in our participants. Now, although we haven't have a chance to do good analyses on them, we have looked at them to see if there is any smoking gun that should be brought before the committee.

So I'd like to show you at least general overall views that were found for the effects on children, adolescents and GI problems. The first thing you'll notice is that the number of children eating olestra at the year one cross-section was about 24 percent of the children we brought in. This compares to the 23 percent we had for the population level use among adults. There is no suggestion that children are eating olestra at any different rate than adults. And this shows mean serum concentrations between consumers and non-consumers. You can see that there is no suggestion of an effect going on there using this very crude look at the data.

In terms of GI reports, now keep in mind this study is not a double blind study. These people know what they're eating. They know, I mean they're reporting what they're eating. That's how we estimate their olestra intake. But we do see here is that, first of all, reports

for nausea, heartburn, gas, diarrhea, are being reported 30 percent of the time or more by everybody, regardless of the amount of olestra intake they have. There is no suggestion of differences for people in terms of how frequently they were sick in bed, went to a doctor for illness or were hospitalized for illness. So there is no smoking gun that we've been able to see in these data.

So in conclusion, our findings from the first year study at Indianapolis is that 15.5 percent of adults actually ate an olestra snack in the previous month, the time we called them with a median frequency of three times a month. We found fairly consistent positive association of olestra intake with serum vitamin K concentrations in both the cross-section and the cohort, and we see no other consistent trends between olestra intake and other fat soluble vitamins or carotenoids, no trends, no associations, no evidence at this time, no suggestion of evidence that there's an association going on.

CHAIRMAN BRANDT: Dr. Peters, you're down to ten minutes and 30 seconds.

DR. PETERS: Thank you. 37 seconds, please. Dr. Tom Ciulla will now present the macular pigment optical density study.

DR. CIULLA: Thank you very much. My name is Tom Ciulla. I'm assistant professor of ophthalmology.

CHAIRMAN BRANDT: You're going to have to talk into the microphone. We can't hear you.

DR. CIULLA: My name is Tom Ciulla. I'm an assistant professor of ophthalmology at Indiana University School of Medicine. I'm a vitra-retinal surgeon with a special interest in macular degeneration research, and my co-investigator is Dr. JoAnn Curran-Celentano. She's a professor of nutrition at the University of New Hampshire and has done quite a great deal of work in this area.

[Slide presentation.]

DR. CIULLA: The main objectives of our study were to determine the major factors associated with macula pigment density in a cross-sectional population sample in Indianapolis. We also wanted to determine whether the past year's intake of olestra was associated with changes in macula pigment density. Dr. Allen Ho has already discussed some of the risk factors for age-related macular degeneration. One of the possible risk factors from macular degeneration is the degree of pigmentation by the carotenoids in the macula. We wanted to determine the factors that ultimately determined the density of the macular pigment and I should emphasize that our study was not a study on macular degeneration but a study on the determinants of macula pigment density in order to hopefully understand the pathogenesis of macular degeneration in the

future.

I also want to point out that our study population was different from the population studied in the Fred Hutchinson trial. Our methods included recruitment of 280 volunteers in the Indianapolis area. The inclusion criteria included subjects aged 18 to 50, and the subjects had to be free of known ocular disease. The measures and procedures during their single clinic visit in order to look at 40 covariates that could potentially determine macular pigment density included, first, measurement of the macular pigment density itself by flicker photometry, dietary intake by one year food frequency questionnaire with snack food addendum, serum carotenoids in vitamin E levels by HPLC, skin color measurements by reflectant photometry, and lifestyle and medical history by questionnaire.

The statistical analysis included multivariate modeling. This slide shows the characteristics of the study population. As you can see, half the subjects were female and half were male. In terms of the ethnicity, the ethnic backgrounds reflect the ethnic backgrounds of the population in Indianapolis in general. You can see that 26 percent of the subjects were current smokers and you can see that we recruited a substantial number of olestra users, approximately 30 percent.

This slide shows some of the key diet and biologic

measures. As you see, the median olestra intake was 0.35 grams per day, and this correlates fairly well with the post-marketing surveillance study. In addition, the plasma levels of lutein and zeaxanthin measured 0.33 microbols per liter which correlates exceptionally well with NHANES III, and finally the median macular pigment density measured 0.21, and this correlates pretty well with the studies that I've done previously although the previous studies were on smaller samples.

This study shows the final multivariate modeling, at least in this preliminary analysis of the data so far. And as you can see, there are several factors that were highly statistically significant in terms of determining the macular pigment density: dietary lutein and zeaxanthin, serum lutein, and eye color. There were other factors that were nearly significant, and they included education and refractive error as well as vegetable consumption.

This plot shows the two factors that were most highly significant: macular pigment density versus serum lutein and macular pigment density versus dietary lutein and zeaxanthin. As you can see, there is a correlation; it's statistically significant. However, there is a lot of scatter, as expected, because these factors only explain a small portion of the variance of the macular pigment density.

Next we analyzed the relationship between macular pigment density and olestra intake. The procedure included adjustment of macular pigment density in olestra for covariates and correlating the adjusted macular pigment density in olestra. What this analysis showed was that there was no significant association of macular pigment density with olestra intake over the previous year. Other analyses were performed including a one-way ANOVA test of macular pigment density, and what you see is that the macular pigment density in the olestra users was virtually identical to the macular pigment density in the non-olestra users.

In addition, two-way ANOVA tests were performed of macular pigment density and olestra correlating for, corrected for gender, eye color, smoking status and race. And again there was no significant difference between the olestra users and non-users. So, in conclusion, this study showed that macular pigment density can be measured routinely in volunteers in a research setting. This had never been done before. In addition, serum lutein, dietary lutein and zeaxanthin as well as eye color are the factors most strongly associated with macular pigment density in a cross-sectional population sample of healthy men and women in Indianapolis.

These factors, however, explain only five percent,

five percent, and two percent respectively of the variance in macular pigment density. Finally, olestra intake over the past year is not associated with macular pigment density in this group. I'd like to thank you all for your attention.

DR. PETERS: Thank you, Dr. Ciulla. I think I have a minute or two left. I'd just like to summarize. Thank you for your patience. We've covered a lot of ground in the last 80 minutes, and I apologize for the tag team but there are so many different people who have been involved, it was important to hear from all of them. We've been through a general review of the literature that has accumulated over the past couple of years in the area of carotenoids and different disease relationships, hearing specifically from investigators involved in these different areas.

We've heard about the active surveillance study that's been up and running now for over a year and has three new sites on line that's ongoing. And finally we've just heard about really a nifty study, I think, looking at using some new methodology to look at pigment density and tissues in the eye. Let me just summarize what I think all of these data point to which is these data continue to support the nutritional safety of olestra, and we've looked, as best we can, under every rock and we've been out measuring and

correlating, and at this time I think this conclusion is a sound thing to say at this point in time. Now, I'd like to open the presentation up for questions.

CHAIRMAN BRANDT: Thank you very much. And if you can gather your folks close to the microphones, that will help us. Okay. We're now open for discussion, questions, et cetera, from this committee. Are there any? And Dr. Benedict.

DR. BENEDICT: I'm sorry. This is for--

CHAIRMAN BRANDT: Dr. Jayhawks deserve representation, too, I guess.

DR. BENEDICT: You're so kind. This is a question for Dr. Ciulla wherever he went. Ah. This is just a small question, but what sort of positive--I'm here--what sort of positive--

DR. CIULLA: I'm sorry. Could you repeat the question?

DR. BENEDICT: I haven't said it yet.

[Laughter.]

DR. BENEDICT: I was sort of waiting for you to arrive.

DR. CIULLA: I was listening.

DR. BENEDICT: Good. Apparently. It's a small question, but what sort of positive control or predictor can you offer us? Suppose macular degeneration and the pigment

differences that you're measuring over a year were actually to take place in two or three years? Do you have some sort of index that you can give us to suggest that you would have picked this up within one year or that you might have to extend the study out for five?

DR. CIULLA: Well, I think your point is very well taken. The study does have limitations. You know it's hard to speculate. I think that olestra has been present in the Indianapolis market for one year. We did recruit a substantial number of olestra users and there appear to be no change at least in that one year test period. Whether there is a change after many years is difficult to speculate on.

DR. BENEDICT: I guess I should have said it more clearly. Are there other changes, similar changes, caused by other disease entities that you'd be able to measure in the shorter term to validate the one year? I don't know enough about macular degeneration to know, but it seems to me that if this is a disease entity that occurs, where is a slope?

DR. PETERS: Perhaps Dr. Celentano would like to comment. There are data where dietary interventions have been looked at for their ability to alter macular pigment density and within a month of feeding a high spinach diet, at least in the Tufts University people's hands, produces a

change upward in some people, not all.

CHAIRMAN BRANDT: You got to make all your comments in the microphone. Otherwise these poor graduate students some day in history will be deprived of your knowledge. Are you through?

DR. CURRAN-CELENTANO: I'm JoAnn Celentano, the other investigator on this study. This was really perhaps best termed a disaster check on olestra on macular pigment density. The study was actually designed to look at what factors influence macular pigment density with the idea that in order to understand if there is a relationship between this carotenoid rich pigment and the disease process, we first need to understand what factors influence that pigment. So the study was actually designed to look at factors that influence the pigment in a population where olestra was part of the choice of dietary factors that the population could make.

It would be very unlikely that we would see a change in macular pigment density, certainly a long way off in looking at disease, but a change in macular pigment density, unless we see a change in serum levels of those carotenoids that make up macular pigment density. And as Dr. Peters had mentioned, there have been a number of studies looking at interventions where you can increase macular pigment density by adding lutein and zeaxanthin

which are the carotenoids of macular pigment to the diet in fairly significant amounts, and we can see increases in macular pigment.

As Dr. Ho had said, there is no good animal model yet or there is no good animal model looking at the disease process, but we don't really know what would happen and how long it would take in order to see macular pigment go down. At this point, we know that macular pigment is fairly stable and that we wouldn't expect to see changes until we see a significant change in serum levels. So that would be the best control that we have as to monitoring the serum levels, but at the same time we are trying to really understand how these carotenoids function in the macular pigment and if, in fact, we can determine the determinants of macular pigment, then we can go further to look at the relationship between these carotenoid rich pigment and the disease process itself.

DR. BENEDICT: So can I just summarize? It has been measured that if you change diet, you can increase, but no one has measured a decrease except as linked with a decrease in serum?

DR. CURRAN-CELENTANO: For all intents and purposes, yes.

DR. BENEDICT: Okay.

CHAIRMAN BRANDT: Dr. Clancy.

DR. CLANCY: Yeah. I have a comment and then a question for Alan Kristal. My comment is that I--and this is not just a legalistic point. I think it's important for Dr. Peters to say that fat-soluble nutrient compensated olestra is safe. We know that in and of itself olestra is not safe, and I think that the numbers that you showed are testimony to the good work that the FDA scientists did in calculating how many of those--at what level those nutrients had to be compensated before olestra could be used.

Question to Alan Kristal is on your last interesting slides, the ones where you were showing us the changes, did you control for exercise or can you show us a table with exercise there?

CHAIRMAN BRANDT: Use the microphone.

DR. KRISTAL: Let's see. I have to say that we have only had these data available to work with for a short period of time, and we have extensive analytic plans, and those data I showed you really are simple cross-sectional, descriptive data, not controlled for anything. I will point out, though, that at least in the cohort, assuming people didn't make other major changes in their lifestyle, they do, I think, represent a true association of, well, at least of olestra or whatever olestra may correlate with. In the cross-section, indeed those data need very careful analysis with control for confounders.

CHAIRMAN BRANDT: Okay. Dr. Byers.

DR. BYERS: In the Indianapolis data that I think basically reassures me that you can do this, so it's sort of a good pilot, there were only 26 people in what you called the high group, which was two grams per day, which if we dose back from the feeding studies, we would expect, in fact, very little effect at that level. My question then pertains to the subsequent study in the other three centers and the three-year follow-up. How will you be sampling or selecting your cohort from the clinical cross-sectional study in such a way that you will enrich that cohort with heavy users?

DR. OMENN: I think what we'll be doing is the same as we did in the cohort here because, let's face it, these are heavy users in terms of this is, I mean the 90th percentile of real use in the real population among people who actually consume it is two grams a day. It's not--

DR. BYERS: In Indianapolis?

DR. OMENN: In Indianapolis.

DR. BYERS: Yeah. My question is in the future. Are you, in fact--how will you select the cohort?

DR. OMENN: Okay. Our method for selecting the cohort, what we did in Indianapolis and what we will do for the future cohort is it's based upon reported intake of olestra snacks during follow-up telephone calls that are

actually currently ongoing that will occur over the next year. So the heaviest consumers, reported consumers of olestra snacks on these telephone calls, will be the people that we will target for selection into the cohort. Now, we designed our cohort to include 20 percent of people who do not report eating any olestra snacks on these telephone calls in order to look at whether, I mean people are going to be changing their intakes over time. Some people will be consistently eating olestra. Some will start and some will stop and some will alternate back and forth.

We want to be able to monitor or to follow whether some people might start eating olestra who do not initially eat it, but the way in which we select our highest use cohort is based upon their reported use during subsequent telephone calls.

DR. BYERS: Could I follow up? Because I think the question of your methodology pertains to your power to look at carotenoid effects in your subsequent larger study, and I'm frankly not clear on this. You do the clinic sample. From the clinic sample, you select your cohort. And my question is how is that done?

DR. OMENN: It is--well, all right. The clinic sample for the three new sites was completed last fall. They all their clinic visits prior to the introduction of olestra. Those people are now being contacted by telephone

for routine follow-up. They're getting three telephone calls per year.

DR. BYERS: All of them?

DR. OMENN: All of them. Based upon the reports on those telephone calls, we will select enough participants, basically we'll collect 600 people that we will target to recruit into the cohorts of that assuming roughly an 80 percent agreement rate. We'll get a cohort of 500 people. And those 600 people will be most--most of them will be people who are reporting the heaviest consumption of olestra. 20 percent of them will be people who do not report any olestra consumption.

DR. BYERS: Okay.

CHAIRMAN BRANDT: Dr. Lamm.

DR. LAMM: Having forgotten my question at the moment, I'll pass.

CHAIRMAN BRANDT: Dr. Fukagawa.

DR. FUKAGAWA: Thank you. I think this may be directed to Dr. Peters. I think your group has done a very good job of demonstrating that fortified olestra has little biochemical effects and that at most you have troublesome GI side effects from consuming 20 grams or more of it. But since we all agree that obesity and its related problems are a significant public health issue for America and potentially the world, one of the big issues is could there

be harm by adding to the food supply something like olestra that may interfere with our ability to educate or appropriately increase the understanding of quote "sound dietary behavior" or food choices for the children or the population in general? And if you would agree that that may be something that is important to address, how do you propose to do so in future surveillance studies.

DR. PETERS: Well, that's an interesting question. I think the data that we have so far would suggest that those individuals who have chosen to incorporate this product into their diets have not made any changes in their diets which would appear otherwise to suggest that they're eating less healthy. They have not changed their intake of fruits and vegetables. They are people who are choosing to consume lower fat foods. You saw the associations between olestra consumption and reduction in total fat in the diet.

There is an association with reduced serum cholesterol. So I don't know how to respond to the what happens in the future? The data we have here and now on people who are actually using this and buying it at the stores and using it in their lives suggests that the people who are making the more healthful choices are the ones who are actually using this product. There is no evidence of over consumption based on the data that Dr. Kristal showed and we have other data from more controlled clinical studies

which show that when people have this as a choice, they don't over consume calories. They do tend to eat less fat and less calories, and if you dilute the caloric density of the foods in the diet, that's likely where you end up. And so I think you end up at the end of the day with a potential net benefit here as opposed to a hypothetical risk.

DR. FUKAGAWA: Except that one--I mean I guess I thought of this question largely in looking at Dr. Kristal's data, in that the numbers really didn't add up in demonstrating that somebody substituted olestra containing low-fat foods for total fat intake. And we know that the imbalance in energy intake that the country is presently experiencing is really rather small and could be accounted for by the difference of three to four grams, well, maybe not that little, but, you know, at least looking at the numbers that you had presented in the graph, and I may have interpreted those numbers incorrectly, but--

DR. PETERS: Well, I'll just say one thing, and obviously the epidemiologists will cringe, but if you look at the associated four percent reduction in percent fat in the diets, in both the cohort and the clinic cross-section, and look at that in a 2000 calorie diet, four percent of that calories would be 80 calories that are lower from fat. That's about nine grams of fat. So given the consumption of the heavy use group, that's about a quarter of the fat

reduction that may be associated with the use of olestra. So all I'm trying to point out is that even with those kinds of associations, a product like this, I mean consider there's ten grams, eight to ten grams of fat in a single serving of a snack food. In a given day, that can be a significant contribution to your daily intake of fat and calories. And so products like this can have a role in helping people to modify their fat intake and to reduce their total daily calorie intake.

CHAIRMAN BRANDT: Dr. Blaner.

DR. BLANER: I have a question, first question about the macular pigment density studies. Has the flicker photometry method for measuring macular pigment density been validated, say, against measurement of lutein zeaxanthin measures in post-mortem eyes?

DR. CURRAN-CELENTANO: Yes. This technique has been established--

CHAIRMAN BRANDT: Get over to the microphone a little closer. Thank you.

DR. CURRAN-CELENTANO: This technique has been well established in both laboratory and some clinical studies as a measure of, indirect measure of the pigment density, the pigment being made up of lutein and zeaxanthin.

DR. BLANER: And does that measure correlate with subsequent occurrence of age related macular degeneration?

DR. CURRAN-CELENTANO: That's the $64,000 question there. No, actually--as I mentioned before, really we're steps away from correlating the relationship or from doing anything other than correlating, making any direct cause and effect relationship between macular pigment and age-related macular degeneration. The pigment is in the area. The pigment lies above the area where the macular degeneration occurs. The pigment is made up of lutein and zeaxanthin, which are two carotenoids. The only source of those carotenoids are diet. The associations between what influences macular pigment density and what influences age-related macular degeneration, there is a good relationship between what goes up and what goes down in both of those pigment density and age-related macular degeneration.

We are still far away from making the association between function of macular pigment and prevention of age-related macular degeneration. The point being in the study that we just completed and are looking at is what factors influence macular pigment density with the idea that if there is an association with the disease process, understanding how that macular pigment is controlled and regulated will ultimately help us in understanding perhaps preventative techniques for dealing with macular degeneration, but we really are quite aways, we're looking at another tissue that we can look at that reflects dietary

trends in carotenoids, but it's really far away from looking at the disease process itself.

DR. BLANER: One last question. Would degree of vascularization of the retina or the back of the eye, I guess, really influence those measures?

DR. CURRAN-CELENTANO: The macular region is an avascular zone.

DR. BLANER: Okay. So it's avascular. Okay.

DR. CURRAN-CELENTANO: Yeah.

DR. BLANER: Thank you.

CHAIRMAN BRANDT: Okay. Dr. Bernstein.

DR. BERNSTEIN: I have a question in terms of since flicker photometry is a somewhat challenging technique both for the researchers and for the subjects, what do you think your sensitivity and power is to detect a difference between your two groups? I mean how much of a change would you need, would you have to see?

DR. CURRAN-CELENTANO: A change between the olestra consumers and non-olestra consumers?

DR. BERNSTEIN: Right or difference, at least.

DR. CURRAN-CELENTANO: Okay. I really can't give you any numbers on that. The one thing I can address is the use of this flicker photometry in this clinic site. We have done a number of studies looking at this in the laboratory environment where we've taken both trained and naive

subjects and done fairly elaborate studies with them. In this situation, we used the technique with a single visit with a slightly modified procedure, and we feel that with the data that we got, where we got the strongest correlations being between dietary lutein and zeaxanthin and serum carotenoids, that the technique is actually working. Perhaps some of the variance or the low variance that we can explain with this procedure at this point may be due to the fact that we have naive subjects running through this macular pigment density procedure.

However, the procedure itself has been validated, and, Paul, you might be familiar with the Maxwellian view system that we've used in the laboratory. We've taken out a lot of the stressful factors and been able to really streamline it so it's not quite as stressful as those of us who have been working on this for years have seen, and we're very pleased with the results of this procedure in this single clinic visit with this technique and feel that this is going to be a way that we can actually incorporate this type of technique into measuring and really understanding macular pigment.

DR. BERNSTEIN: Do you have plans for looking at prospective effects of olestra?

DR. CURRAN-CELENTANO: It's in the thought process at the moment.

CHAIRMAN BRANDT: Dr. Applebaum.

DR. APPLEBAUM: Dr. Ciulla--I don't mean to mispronounce your name, and I apologize, from what area of the country did you take your population?

DR. CIULLA: From Marion County, Indianapolis.

DR. APPLEBAUM: Oh, okay. So the same. Okay. All right.

DR. CIULLA: I mentioned it was a different population. What I meant to say they were different subjects. The subjects from our study were not the same subjects that were assayed by the Fred Hutchinson group. But from the same general population of Marion County.

DR. APPLEBAUM: Okay. I was wanting to draw some type of conclusion to what appears to be what is customarily consumed, i.e., actual amounts. You know we talk about two grams per day at the highest, you know, ten percent. You found 5.8 grams at the five percent, five percent of the population that was consuming quote-unquote "the highest amount." I like the data that present what is actually consumed. So I was wondering if yours was from a different part of the country, but, no, it's the same, essentially the same set of or the same quote-unquote "universe" that you're pulling from.

My question then is for Dr. Thornquist. Did you, one of your concluding remarks--at least this is what I took

from it--is that as olestra increased, you saw higher levels of serum vitamin K.

DR. THORNQUIST: Right.

DR. APPLEBAUM: Okay. Would you comment on that further?

DR. THORNQUIST: What--

CHAIRMAN BRANDT: If you're going to comment on it, do it in the mike.

DR. THORNQUIST: What specifically do you want me to comment on?

DR. APPLEBAUM: Okay. I guess I'm looking--my conclusion is--I am drawing a conclusion when you say as olestra increases, you're having higher levels of vitamin a--vitamin K--excuse me--in the serum.

DR. THORNQUIST: Okay. That association is what we saw in the data.

DR. APPLEBAUM: Okay. Would anyone on the panel at this point in time want to speculate as to what? Olestra is currently being compensated with vitamin K; am I correct?

DR. THORNQUIST: Overcompensated.

DR. APPLEBAUM: Okay. So I'm not leading myself into a wrong direction?

DR. PETERS: No. That's correct. Olestra contains vitamin K at about one RDA per serving, and as Dr. Thornquist pointed out, the data are preliminary with the

error bars being what they are, but the trend seemed consistent. It certainly suggests that the amount that's in there is enough to compensate for any olestra effect, and it's certainly possible that there's a little bit more in there.

DR. APPLEBAUM: But the differences weren't biologically significant?

DR. PETERS: Right. It was about a mean of 15 percent at the highest, you know, across the levels where it was above the line, it's about a 15 percent increase in the serum level.

DR. APPLEBAUM: Okay.

CHAIRMAN BRANDT: Okay. Dr. Clancy.

DR. CLANCY: I think I know the answer to this question. It goes to Dr. Kristal again or any of you. You probably have not been able to do the analysis of dietary supplement use against any of your populations yet? Is that true?

DR. KRISTAL: Actually we have analyzed the dietary supplement information that is to control for the multi-variant models that looked at the serum levels. So indeed we have from the food frequency and the supplements combined used those numbers in our models.

DR. CLANCY: But have you done that against the data you presented? For example, when I asked you--it's the

same question I was asking you about exercise.

DR. KRISTAL: Oh, you mean what's the relationship between exercise and olestra consumption--

DR. CLANCY: Right. And dietary supplements, yeah.

DR. KRISTAL: --vitamin supplement use and olestra consumption?

DR. CLANCY: Right.

DR. KRISTAL: Actually I do have those results if we could come back to it. I just need to pull it out of a report.

CHAIRMAN BRANDT: Dr. Crouch.

DR. CROUCH: This is a question about the AMD study. I wondered why you limited it to subjects 50 and younger and do you have plans to look at people more in the range of people who actually get the disease?

DR. CURRAN-CELENTANO: Okay. I can answer that by this was not an AMD study. This was a macular pigment study. We purposely chose a younger population because we did not want them to have ocular disease because we're looking at the factors that influence macular pigment. In the future, if we're looking at the disease process, obviously we need to go into a higher population. We would not expect macular degeneration to occur in this age population, so in the fact that we were just looking at the

influences of macular pigment with the ultimate idea that we might look at disease, we chose the younger population.

DR. OMENN: The result was they got terrific range of values for the ocular, the density measurement. So it should be sensitive for this study.

CHAIRMAN BRANDT: Did you find the slide you want?

DR. KRISTAL: I did. [Slide.] I saw a slide. I can just tell you what the numbers were if you'd like to know. The average, 47.9 percent of the population used any kind of dietary supplement. And the range, the numbers were not statistically significant. They're going from none, low, medium, high. They go 46.5 percent, 51.2 percent, 48.4 percent, 55.6 percent.

CHAIRMAN BRANDT: Okay. All right. Dr. Byers.

DR. APPLEBAUM: None of it's significant.

DR. KRISTAL: No, this is random variability.

CHAIRMAN BRANDT: Dr. Byers.

DR. BYERS: Have you at this point done any analyses looking at the consumption of olestra with or without foods in the previous month before the blood draws. I know you just got the data recently, but you have tooled up to do this. You have the software to do it. Have you taken a look at that lately? And the reason I ask obviously is because the clinical trials that were done to date showed rather marked effects in two weeks when it was consumed with

all meals.

DR. KRISTAL: Let me ask that back so I understand what you're asking. You're asking about when the olestra was consumed before measured the serum levels?

DR. BYERS: Yeah. Your analyses indicated say two grams per day on average was the high dose. But have you done any analyses at this point looking at cholesterol consumption in the last week or two or three or four with or without foods?

DR. KRISTAL: No.

DR. BYERS: You have the capacity to do that in the future.

DR. KRISTAL: No, we have the capacity to estimate the population level consumption of carotenoids with and without olestra because it's from 24 hour dietary recalls. It's from a single day. So we can get a population level estimate of the percent of the carotenoids that disappear in the population that are co-consumed with olestra, and I can tell you that. Well, actually I can't tell you that number because it's so small we couldn't calculate it.

We do have an overhead--if you'd like to see an overhead, we can show you. But the recency of olestra consumption, which is, I think, the question you were asking?

DR. BYERS: Do you have the capacity to do that in

the future?

DR. KRISTAL: No.

DR. BYERS: That's a more important question than have you done it in the Indianapolis data. In the future, will you be able to do analyses--

DR. KRISTAL: No.

DR. BYERS: --in which you look at--

DR. KRISTAL: No, that--

DR. BYERS: --recency of intake with or without foods as related to blood levels?

DR. KRISTAL: Not without significantly changing our protocol in a way that I think would be unfeasible. That would require--

DR. BYERS: I thought your dietary assessments included that feature.

DR. PETERS: The assessments--both the 24 hour recalls done just before the blood drawn and then the previous month's intake by food frequency questionnaire where questions are asked about co-consumption can be used to look at that question, and because the carotenoid half-time in the blood is such that you wouldn't expect to see a steady state level with people who are using it regularly until two weeks to a month, as you pointed out, looking at--that's why we designed the food frequency to look over the previous month as opposed to farther retrospectively because

we're sort of gearing it to the biology of the carotenoids.

And so we do have the ability to do that. And I think the preliminary data looking at just percent co-consumption of carotenoids with olestra are very consistent with the modeling that we had done prior to approval which is it's a fairly low frequency event when it is a snack food. But, you know, that's part of what we're learning from the real marketplace.

CHAIRMAN BRANDT: Dr. Chassy.

DR. CHASSY: I know we're not supposed to ask anything that relates to earlier data, but it seems to me that we saw some earlier data--

CHAIRMAN BRANDT: But in spite of it, you're going to.

DR. CHASSY: Yes. Because it relates to the vitamin K changes. Did we not see earlier data that indicated that you would expect that when fat soluble vitamins were taken in low amounts in the diet that you would expect the compensated fat-soluble vitamins in the olestra to come out of the olestra, and when you had a diet that was high in fat-soluble vitamins, you might expect the net flux into the olestra? Is that a correct recollection?

DR. PETERS: That's a pretty good synthesis. The vitamin restoration levels were determined in order to deliver for the population as a whole an adequate level. So

that if you were consuming on average much, much less than that, then the snacks might provide a little bit net vitamin. You know if you were taking a supplement or something and were way up there, then it wouldn't get you all the way back up there if you ate it at the same time, but it was preserving the overall--

DR. CHASSY: Okay. Well, then the follow-up is when we saw these fat-soluble vitamins, we saw them plotted, if I recall correctly, as percent changes, as differences, and what I'd be interested in seeing or knowing whether you've looked at is the absolute values to see whether, for example, in the high consuming groups, whether the absolute serum value was lower and whether what you were doing by adding olestra was supplementing them with vitamin K. Have you looked at that?

DR. PETERS: Well, you can look at that. The cross-sectional data that were shown from the Indianapolis site were actually plotted as concentration units, whereas the cohort was a percent change and in both cases you saw the same trend for vitamin K.

CHAIRMAN BRANDT: Dr. Clydesdale.

DR. CLYDESDALE: Yes. For Dr. Thornquist, after one year the baseline seemed to vary with the serum levels up and down, and were more of them down than up and were the levels of variance to be expected across that baseline?

DR. THORNQUIST: What you're talking about is the serum levels in the non-consumer group compared to--

DR. CLYDESDALE: Yeah. Just the line across.

DR. THORNQUIST: I think there may have been numerically more that were down than up. I don't think it was a statistically consistent pattern.

DR. CLYDESDALE: You mean they went down for non-users as well as users; right?

DR. THORNQUIST: I guess now I'm confused what you--can you rephrase the question?

DR. CLYDESDALE: Okay. Can we see one of the slides maybe and maybe that will help me?

DR. THORNQUIST: Sure.

CHAIRMAN BRANDT: Which slide do you want to see?

DR. CLYDESDALE: The after one year.

DR. THORNQUIST: So do you want the cross-section or the cohort? Well, it would have to be the cohort--

DR. CLYDESDALE: Yeah, right.

DR. THORNQUIST: --because the cross-section doesn't compare to this one.

DR. CLYDESDALE: That's right. That's right.

DR. KRISTAL: Slide 61.

CHAIRMAN BRANDT: You're talking about carotenoids now?

DR. CLYDESDALE: Yeah, or any of the other levels.

I mean, you know.

CHAIRMAN BRANDT: Any of the other levels. Okay. Is that what you're looking for?

DR. CLYDESDALE: No, no, keep going. No, that's--

DR. THORNQUIST: Well--

CHAIRMAN BRANDT: Right there?

[Slide.]

DR. CLYDESDALE: Yeah, okay. Yeah, that's fine. Just the baseline levels are down, for instance, although the vitamin K is trending up, the baseline is down to minus 20; right?

DR. THORNQUIST: Right.

DR. CLYDESDALE: And the baseline is down with the vitamin D and a little bit down for retinol. But I guess I'm asking is that expected over a year? I mean is that--

DR. THORNQUIST: No, we would not have any reason to expect that to be a true, to be a real effect. I mean we've incorporated age as predictors in these models and we don't get changes of that magnitude associated with a single additional year.

DR. CLYDESDALE: I was wondering do you have any-- because we saw that; right? Do you have any ideas why that's happening or?

DR. KRISTAL: Well, vitamin D obviously because of sunlight.

DR. CLYDESDALE: Well, I mean--yeah, but the others. I mean if you can show another slide.

DR. KRISTAL: Vitamin K is responsive to what's eaten in really the very brief period of time. So random variability on that one is a big guess.

DR. CLYDESDALE: Okay. Can we see the carotenoids?

DR. KRISTAL: Sure, if you'd advance it one more slide.

[Slide.]

DR. CLYDESDALE: So the others are just--

DR. KRISTAL: So alpha-carotene is a little up. Lutein is down. Beta-carotene is a little down. Total carotenoids are very slightly down.

DR. CLYDESDALE: I was just wondering whether this was in limits which one would expect or anticipate?

DR. KRISTAL: It's just random.

DR. CLYDESDALE: Okay.

DR. KRISTAL: It's relatively small considering it's just random change.

CHAIRMAN BRANDT: Dr. Blaner.

DR. BLANER: I have a question about the carotenoid measures. Your total carotenoids--first question--total carotenoids are just the sum of the six individual?

DR. THORNQUIST: That's correct.

DR. BLANER: Okay. Question. There's a small amount of literature, but it seems to be growing, that within humans at least for beta carotene consumption, that there is this concept of responders and non-responders, that some individuals absorb well, and others may be absorb less well. Did you look at your data from that perspective? You presented the data as a function of olestra use. If you looked at just individuals which had the lowest ten percent of carotenoid levels--and I'd also like to ask this for all the true vitamins--whether there was any differences just looking at that lowest ten percent of levels?

DR. THORNQUIST: We have not done analyses of that sort so I can't say if there is any difference in them.

DR. KRISTAL: I could say with regression to the mean I can tell you exactly which direction they go.

CHAIRMAN BRANDT: Okay. Dr. Underwood.

DR. UNDERWOOD: Thank you. Am I correct that your active surveillance is only from above five years of age?

DR. THORNQUIST: Actually it's seven years of age.

DR. UNDERWOOD: Above seven. So you're not really following younger children in this?

DR. THORNQUIST: That's correct because we couldn't do, we couldn't assess their dietary intake which is the biggest predictor of their serum levels with any

accuracy with children that young.

DR. UNDERWOOD: Well, then my second question relates to the vitamin A serum levels, which are not really very reflective of vitamin A status. So I'm wondering about using particularly means to monitor that, and I would kind of reinforce what Dr. Blaner just said that you might want to look at those data on a distribution rather than looking at means for surveying--

DR. THORNQUIST: Okay. Although actually since, I mean what's presented there are geometric means. So they are more closely approximating the median.

DR. UNDERWOOD: And then my last question relates are you getting any information on patterns of intake, whether it's snacking versus meals as related to monitoring serum levels?

DR. THORNQUIST: Yes, and Ruth is looking up that information.

DR. PATTERSON: We do have data on that. I can't address olestra in particular because this is from a validity study we did on our instrument called the focused recall.

[Slide.]

DR. PATTERSON: And of the 500 recalls we had only, let's see, there were only nine instances of eating olestra. So I can't really say anything about olestra. We

did look at what I think you're asking, the pattern of eating snacks, when do they mostly eat them? So for all savory snacks, let's see, we found that about one percent were eaten at breakfast, about 18 percent at lunch, ten percent at dinner, and 23 percent was snacks that would unlikely be consumed with anything else. This might actually answer your question a little better, based on that same study.

[Slide.]

DR. PATTERSON: So this again was from our validity study on the co-consumption of carotenoids with savory snacks. The focused recall is the new instrument developed. A 24-hour recall is just the traditional everything you ate in the past 24 hours. This is on 500 participants where we administered the focused recall and then administered the 24 hour recall, and for the 24 hour recall, we developed a set of computer algorithms that actually click through the day and anytime somebody ate a savory snack, if carotenoids were consumed within an hour plus or minus one hour, then that was considered co-consumed. We can change that period of time to any period of time we want, but that was just where we started, and using that approach to asking this question, we found--let's just look at the 24 hour recall column--that overall about 13 percent of total carotenoids were consumed at the same--I

should say the same occasion as some type of savory snack and that includes chips and crackers and even pretzels. So it's a pretty broad definition of a savory snack.

Among full-fat snacks, six percent were consumed at the same time of carotenoids, consumed at the same time. And then 70 percent as reduced or non-fat. Given the information that we have to date that suggests that olestra eaters are mostly people replacing non-fat snacks or low-fat snacks, that seven percent figure to date is probably our best estimate of at-risk carotenoids over the population in a single day.

CHAIRMAN BRANDT: Okay. Thank you all very much. Appreciate your being here. You've come from all the country. It's kind of a--I wanted to ask one question about whether or not you had any colts in the Indianapolis study, but I won't do that.

[Laughter.]

CHAIRMAN BRANDT: We'll now turn to the CSPI presentation. You've got 40 minutes. Dr. Jacobson.

DR. JACOBSON: Good afternoon. While our comments will focus mostly on carotenoids today, I want to begin by discussing two possible adverse effects of olestra suggested by adverse reaction reports and other data.

[Slide presentation.]

DR. JACOBSON: First, CSPI and Procter & Gamble

have received numerous reports of hives and similar symptoms. In a sample of 1317 reports to Procter & Gamble, 32 people or 2.4 percent reported hives. In a series of 398 reports to CSPI, five people, or 1.3 percent reported hives. At least ten of those people have such severe reactions that they went to the emergency room or called the doctor.

The hives usually occurred without accompanying GI symptoms, and the affected individuals generally did not have a history of allergies. This issue deserves further research to establish whether olestra chips for whatever reason can cause hives. And if that link is demonstrated, the label notice should mention hives.

The second issue has to do with the interference with the absorption of prescription drugs. CSPI received an adverse reaction report from a nurse who reported that her oral estrogen replacement therapy had been an effective treatment for three years. Three weeks after she began eating a 5-1/2 ounce package of Wow chips two or three times a week, she started reexperiencing menopausal symptom including hot flashes and mood swings. She consumed an average of about 16 grams of olestra per day.

Her nurse advised her to stop eating the chips and to switch her estrogen from a pill to a patch, thus avoiding potential interference by olestra in the GI tract, and her symptoms disappeared immediately. Furthermore, a 1994 rat

study not sponsored by Procter & Gamble found that a sucrose polyester similar to olestra substantially reduced the absorption of cyclosporine, an important immunosuppressant drug that is taken by transplant patients and used for other purposes. P&G appears to have conducted only two human studies on drug absorption. Both tested only moderate doses of olestra and both were negative. The better study on oral contraceptives tested only 30 women who consumed only 18 grams of olestra per day.

It's possible that at least in some people, olestra would affect the absorption of oral contraceptives or other drugs. Committee members have a letter concerning olestra and drug absorption from the University of Texas professor of pharmacology, Robert Talbert. Dr. Talbert urged this committee, and we passed out a revised addition of his letter this afternoon. Dr. Talbert advised the committee, quote: "At a minimum, require the manufacturer to conduct scientifically sound clinical trials of olestra in larger doses to determine if the risk of drug malabsorption is real."

I'd like now to turn to the carotenoids issue. Several significant developments occurred shortly before the FDA's approval of olestra and then subsequent to the approval a consensus has developed that carotenoids likely provide health benefits to humans. Prior to the 1995 Food

Advisory Committee, but the committee was unaware of it, the FDA invited USD nutrition researcher, Walter Judd, to review Procter & Gamble's eight week studies on olestra.

Dr. Judd responded with a sharply worded memo that was not shared with the committee or discussed in the Federal Register notice approving olestra. He concluded that quote, "potentially detrimental effects of olestra on absorption of essential fat soluble nutrients lead this reviewer to include that olestra cannot be safely added to the diets of very significant portions or numbers of the U.S. population. Benefits that might be gained by a few people by the consumption of fat-free or fat-reduced snack foods appear\e illusionary and certainly do not justify the potential risk of detrimental health effects for many others.

Since January 1996, a consensus has developed that carotenoids are likely to reduce the risk of chronic diseases. Days before olestra was approved, the U.S. Departments of Health and Human Services and of Agriculture released a new edition of dietary guidelines for Americans. That pamphlet urges Americans to consume more foods rich in carotenoids and other anti-oxidants quote "because of their potentially beneficial role in reducing the risk for cancer and certain other chronic diseases. Evidently, the two federal departments believe that despite lack of proof that

carotenoids provide benefits, the evidence is so great that the public should be encouraged to consume more foods rich in carotenoids.

Second, on January 17, 1996, Dr. Walter Willett convened a workshop at the Harvard School of Public Health that focused on the effect of olestra and carotenoids. That meeting involved experts on diet and chronic disease including Mark Hegstead, George Blackburn, Norman Krinsky and others. Procter & Gamble sent its representatives. At the end of the workshop, there was a general consensus excepting Procter & Gamble that carotenoids are likely to be beneficial and that olestra does not meet the reasonable certainty of no harm standard.

Third, after the approval of olestra, the National Cancer Institute stated numerous studies have found evidence that carotenoids reduce the risk of some cancers. The evidence is particularly strong for lung cancer.

Fourth, in late 1996, the American Cancer Society's new nutrition guidelines stated that anti-oxidant nutrients which include carotenoids are thought to protect against cancer.

And fifth, in 1997, the World Cancer Research Foundation advised that diets high in carotenoids probably reduce the risk of lung cancer and possibly decrease the risk of several other important cancers. Clearly, the

scientific community has reached a consensus that carotenoids are likely to reduce the risk of cancer and other chronic diseases. Procter & Gamble certainly cannot show that there is a reasonable certainty that lowering carotenoid absorption is not harmful.

Now, I'd like to turn the microphone over to Dr. Graham Colditz, a professor of medicine at the Harvard Medical School, who will discuss olestra and carotenoids in greater detail.

DR. COLDITZ: Thank you. Walter Willett is out of the country today, and so I'm here. I'm here in part representing the views of the department of nutrition at Harvard School of Public Health, a group with which I mark. I've not been funded by Procter & Gamble. I can't drink their coffee, and in fact, the nutrition department endowment has paid for my expenses here. If we can go forward--are we on?

[Slide presentation.]

DR. COLDITZ: To follow up on Michael's point, as he concluded, carotenoids have health benefits and I will show you some of that data this afternoon. Uncertainly about these health benefits justifies further research and I will conclude mandates informed consent for interventions. Few can review the evidence objectively and conclude that there is reasonable certainty of no harm.

In terms of new evidence, I will run through several studies. I had the executive summary of the Procter & Gamble documents so most of my comments on their document relate to the executive summary. I have worked to avoid selective citation. We've searched the literature from January 1996 forward and discussed with colleagues to identify other relevant pieces of information. I'll first review this evidence, then present estimates of the potential disease burden and finally conclude with a critique of the Procter & Gamble submission.

If we turn to lung cancer, Regina Ziegler from the National Cancer Institute drew on the NCI funded database to look at specific carotenoids. She reanalyzed her case control study and in so doing found significant relations for carotenoids. And I want to emphasize now and throughout that we should not focus solely on beta carotene or use it as a fog screen for some 500 other carotenoids as well.

In her reanalysis of the case-controlled study including 523 cases, among current smokers and recent past smokers, she saw a significant relation that has over a two-fold higher risk for participants in the lowest 25 percent of alpha-carotene with a significant dose response. P equals .004. For beta carotene, she saw again a significant dose response with a relative risk of about 1.6. And likewise for lutein.

In terms of fruit and vegetables, these were also compared to the carotenoids, and importantly the alpha-carotene response is far stronger than that for fruit and vegetables. So these data, while not conclusive, are new since 1996 and provide a basis for reasonable certainty of no harm.

The Procter & Gamble statement on this study in the executive summary says that where comparison was made, the inverse association between fruit and vegetable intake and lung cancer was stronger than that of beta carotene. This statement is made despite the alpha-carotene result that I just showed you and as I've said, I believe the emphasis on beta carotene obfuscates the overall evidence on carotenoids as a whole.

Now, there are additional lung cancer data. The follow-up of the NHANES cohort has been published back in 1997, 19 year follow-up, 248 lung cancers, and carotenoids were inversely significantly related to lung cancer risk. The multivariate relative risk comparing the top 25 percent to the bottom 25 percent of intake showed approximately a 25 percent reduction in risk, and the trend was statistically significant.

A cohort of men and women in New York followed over seven years has also been published in Cancer Causes and Control. Carotenoid intake was significantly inversely

related to risk of lung cancer among men but not among women.

For prostate cancer, several studies were discussed in the summary from Procter & Gamble, and I will come back to that, but importantly there have been studies presented at scientific meetings this year, and the largest of these is from the Physicians Health Study where the abstract is available. In this study with some 580 cases of prostate cancer in participants in the trial, some 16,000 who provided blood samples before they were randomized have been followed, and the cases of prostate cancer confirmed.

Of all the carotenoids looked at, alpha-carotene, beta carotene, lutein, in adaptation to alpha-tocopherol, gamma-tocopherol, retinol, and so on, the only carotenoid that came through significant was lycopene, and this, of course, is consistent with work that our group has published previously for dietary intake in a separate study.

The relative risk shows stronger protection against advanced disease, some 259 cases of disease that had spread beyond the prostate, monotonic decreasing risk with increasing baseline blood lycopene levels, 60 percent lower risk in the highest 20 percent of lycopene blood levels. The relation was also stronger for cancers diagnosed within the first six years after blood draw than in those diagnosed in the subsequent seven years.

Putting this in context of all the evidence on lycopene and cancer, there are now some 66 studies that have reported on either the intake of the tomatoes, tomato-based products, lycopene, examined blood levels of lycopene, and related one of these measures to risk of cancer. 52 of 66 report inverse associations and some 32 of these associations are statistically significant. The data are most compelling for prostate, lung and stomach cancer. While not conclusive, these new data do not provide a basis for reasonable certainty of no harm from reducing lycopene levels.

Let's turn to breast cancer. An abstract in the American Journal of Epidemiology this year summarizes updated analysis from the Nurses' Health Study. Using 14 years of follow-up from when diet data were first collected in 1980, we have confirmed 784 premenopausal cases of breast cancer and just under 2,000 post-menopausal cases.

The strongest and significant result observed was among premenopausal women, and I believe this is important because elsewhere we're being presented with results drawn from post-menopausal women where we and others see far less effect for carotenoids. In our analysis, lutein and zeaxanthin, carotenoid vitamin A and total vitamin A from foods were each significantly related to lower risk. The relative risks were stronger in premenopausal with a family

history of breast cancer and those consuming 15 or more grams or alcohol per day, two groups of women who, of course, are from our population at higher risk of premenopausal breast cancer.

Among those with a family history, again, a monotonic relation was seen with increasing carotenoid intake here, and the relative risk comparing the highest quintile to the lowest quintile of intake showed a 60 percent lower risk with a p for trend of .001.

Data on serum carotenoids and carotid artery disease have also been published. Here drawing from the AIRC study funded by the NIH, the atherosclerotic Risk in Community study, carotid artery intimal thickness has been a major feature of that study, and it has in large part documented that this is one of the most powerful predictors of both stroke and heart disease, really integrating cardiovascular risk factors in the study published by Iribarren and Folsom and others from that collaborative work, published in 1997 in the Journal Atherosclerosis, Thrombosis and Vascular Biology.

The beta cryptoxanthin and lutein plus zeaxanthin were significantly inversely related to the extent of the atherosclerosis and a one standard deviation increase in those carotenoids was associated with a 25 percent lowering in risk based on this carotid artery intimal thickness.

While not conclusive, new data here do not provide a basis for reasonable certainty of no harm from lowering carotenoids.

Data on lipid peroxidation have also been published. A standard marker of lipid peroxidation has been examined in 25 cystic fibrosis patients who have fat absorption problems that have been supplemented with beta carotene which normalize the levels of the marker for lipid peroxidation, and that, in fact, supports a range of previous studies among children with cystic fibrosis. Lepage American Journal of Clinical Nutrition 1996. Lipid peroxidation has also been studied in a placebo controlled, double-blind study conducted in the Western Human Nutrition Research Center and published in JACN 1998, pages 54 onwards. Some nine premenopausal women were randomized to depletion from carotenoids for 60 days verse the placebo control. Carotenoids were added back. While they were on the depletion their MDA levels rose showing significant deterioration in their peroxidation levels. When the carotenoids were added back from day 60 to 100, they levels returned to the same as the placebo group.

If we look at cataracts, we are able in our health professions follow-up study to examine diet and risk of subsequent cataract extraction, drawing on data from over 36,000 men. Cataracts develop at least in part due to

oxidative damage to the lens proteins and lutein is both an effective an antioxidant and may be uniquely important since it is the only carotenoid found in the human lens. Again, these data published in abstract form and available to everyone show lower risk among men with higher intakes of lutein and zeaxanthin but no other carotenoids in the diet. A p for trend across increasing levels of intake. P equals .04. About 20 percent lower risk of cataract extraction in the men with the highest level of intake.

Again, while not conclusive, these new data do not provide a basis for reasonable certainly of no harm with further reduction in carotenoid levels. How do we place these in perspective? The report from the Food, Nutrition and Prevention of Cancer, a committee of the World Cancer Research Fund and the American Institute for Cancer Research published in 1997, in fact, indicates that there is no convincing evidence that carotenoids are associated with decreases in risk of any cancer. That lung cancer, there is a probable association. They do not mention beta carotene. They talk about carotenoids in general, and likewise for a possible relation for esophagus, stomach, colon and rectum, breast and cervix. Notice that there is no data at all showing increases in risk with these general carotenoids.

What are the sort of data behind their conclusion published last year? In fact, there are many studies. For

example, four or five diet cohort studies show the relation for lung cancer, while six of six serum studies do, and 16 of 17 case control studies support that conclusion. And so on. You can go down and see a consistent set of data supporting the recommendations and conclusions of that committee. Again, they were reporting on carotenoids in general, not on beta carotene.

To provide further evidence on expert opinion regarding carotenoids, Walter Willett conducted a survey of 13 members of the 1982 Diet and Cancer Committee of the National Academy of Sciences. He posed two questions to them on a written questionnaire. This was mailed to them in 1996. Are you reasonably certain that carotenoids contained in fruits and vegetables are not related to the apparent benefits of these foods in reducing cancer risk, he asked?

Are you reasonably certain that reduction in blood levels of carotenoids will not increase the risk of cancer? Two of 13 members did not respond. Three responded but indicated that they did not want to answer those questions. None answered yes to either question, and eight of the 13 answered no to both questions. So there is some consensus in the scientific community that carotenoids are likely to reduce the risk of cancer and other chronic diseases. Note as Michael has already summarized, there are numerous other recent recommendations from the American Cancer Society,

U.S. dietary guidelines and so forth that support this position.

Now, we've seen these data before the reduction in carotenoids when the standard data from eight grams a day of the Procter & Gamble product or three grams a day in the paper by Westrate showed the approximate 60 percent reduction in carotenoids here in the U.S. data, 40 percent for total, 50 percent for total carotenoids. We can use this as a starting point to estimate the potential impact of carotenoid lowering given widespread consumption of olestra. And these calculations were done after several discussions really following on work that Jeffrey Rose has done in the past to look at cardiovascular impact of small changes in population levels. We assumed, as Procter & Gamble had asked, that a large portion of the snack market was using olestra and estimate that the average reduction in carotenoid levels should that be the case of widespread use in the U.S. would be approximately ten percent.

This is based on the 60 percent reduction in total carotenoids from the feeding study I just showed plus estimates of light snackers eating three snacks per week and heavy snackers eating six snacks per week containing olestra. So if that level of widespread consumption is achieved through appropriate marketing, what would the disease burden likely be?

We fit a regression to the relations between carotenoids and the different diseases, assuming a linear relation, as this is consistent with the epidemiologic data that's been summarized to date. And then we estimate the change in risk for a ten percent change in carotenoid levels. These are the data that you've already heard referred to. Assuming the lycopene prostate cancer relation is real and causal, the ten percent reduction based on the dietary data would give about a one percent increase in the rate of prostate cancer, which is 2,400 additional cases of prostate cancer per year.

If we go with the strength of the relation seen from the serum study, we'd actually see a four percent increase in the rate of prostate cancer, almost 10,000 additional cases per year. For coronary heart disease, for a ten percent reduction in total carotenoids, we'd see a nine percent increase in the rate of heart disease, 32,000 additional deaths, lung cancer, a variable estimate between two and ten percent increase in the rate of lung cancer, translating to anywhere from 1,400 to 1,700 additional cases of lung cancer per year. And for macular degeneration, probably the least certain of all those on the screen here, some 390 additional cases of blindness per year.

This is, in essence, the size of the gamble we are contemplating here today with widespread use of olestra. So

even small changes of the population level in terms of mean concentrations of carotenoids in the blood can translate into substantial disease burden for the total population. This is a well known public health construct that's been evident for heart disease since Rose emphasized this relation years ago.

If we turn to the Procter & Gamble review, I would argue that the executive summary contains selective citation of the literature, is extensively focused on beta carotene to the exclusion of other carotenoids and omits numerous reports, as I've already attempted to show.

With regard to prostate cancer, the report concludes that new studies have not corroborated the hypothesis by Giovannucci that dietary lycopene protects against prostate cancer. And heavy weight is placed on the Hawaiian data which is based on 22 years of follow up and in fact a lack of association up to 22 years after a single blood draw is, in fact, consistent with the data from the physicians trial where stronger results were seen in the first six years after blood draw suggesting that the effect for lycopene is very late in the progression to aggressive disease.

For breast cancer, Procter & Gamble state serum carotenoid concentrations were not also associated with reduction in risk of breast cancer in two case control

studies and they cite Dorgan, '98, and Burgaz, '96.

If we turn to Dorgan, '98, what do we see in the abstract? Serum lycopene was also associated inversely with risk and among women who donated blood at least two years before diagnosis, a significant gradient of decreased breast cancer risk with increasing lycopene concentration was evident. A marginally significant gradient of decreasing risk with increasing serum lutein also was apparent. Apparently that wasn't significant as far as they were concerned.

And these are the data. We actually see that for the lycopene where somewhere around a 60 percent lower risk in the highest 25 percent of the blood levels and p for trend is .02, highly significant, and the lutein approximately a 40 percent lower risk.

Upper aerodigestive tract cancer, also from the Hawaiian data, which were good to cite for the lack of relation with lycopene, were apparently omitted. And they, in fact, show a strong inverse relation between carotenoids and this cancer. This is how strong the relation is. 80 percent lower risk in the highest one-third of carotenoid levels compared to the lowest one-third of carotenoid levels, statistically significant.

While not conclusive, these new data do not provide a basis for reasonable certainty of no harm by

lowering carotenoid levels.

In terms of cardiovascular disease, observational intervention data, they say have been negative and does not support a role for carotenoids and protection from cardiovascular disease. Meanwhile, Kohlmeier published a study with approximately a 50 percent reduction in risk comparing lycopene levels in the EURAMIC study. These were first heart attacks that were hospitalized. A subcutaneous fat sample was taken to give a long-term measure of carotenoid exposure that would not be influenced by the events of the heart attack, and both beta carotene and lycopene were significantly inversely related to risk of myocardial infarction.

The lycopene here in yellow with a p for trend of .008 and the beta carotene in red actually also having a significant test for linear trend of .023, and both of those were significant when the two carotenoids were simultaneously included in the analysis.

Now, Peter Greenwald's letter has been circulated to you, and again it focuses solely on beta carotene, and I do remind you that Regina Ziegler, also with the National Cancer Institute, can speak with authority on a broad range of carotenoids, and I've showed you her data with alpha-carotene strong inverse relation with lung cancer risk.

In conclusion, few can review the evidence

objectively and conclude that there is reasonable certainty of no harm from reduction in carotenoid levels. There is uncertainty and incomplete understanding. There is no certainty of no harm due to reduction in carotenoids. Where does that leave us?

One could reasonably conclude with these data that olestra should not remain in the food supply. If it is in the food supply, a label should say it is there, and as Walt Willett has emphasized, we might continue with the warning that says olestra reduces absorption of carotenoids. Low intake of carotenoids has been associated with increased risks of heart attacks, strokes, cancers of the lung, breast, prostate, esophagus, stomach and uterus, cataracts and degenerative changes of the eye that can lead to blindness. Thank you.

CHAIRMAN BRANDT: Dr. Jacobson, do you have more?

DR. JACOBSON: No, that concludes our presentation. We greatly appreciate it.

CHAIRMAN BRANDT: Thank you very much. Appreciate it. Can you turn up the lights now so I can see what I'm doing? Thank you. We're going to open this up for questions, but I have one for Dr. Jacobson who talked about the consensus with HHS, Cancer Society and so forth. I sit on the Secretary's Advisory Committee on the Year 2010 Objectives, and I also until a month ago sat on the board of

the Heartland Division--that's out in the heartland of the country--of the Cancer Society. The information we were provided at the last meeting a month ago of the Secretary's Advisory Council was that the issue was eating more fruits and vegetables. It didn't say a word about carotenoids.

The same was true with the Cancer Society, and I'm wondering whether you're extrapolating or whether I just didn't get all the information, and if so, I'd like a copy of the HHS material?

DR. JACOBSON: I don't have a copy of Dietary Guidelines for Americans with me. But it was very clear that carotenoids in particular were mentioned, and there was even a chart. The only chart, as I recall, in the fruit and vegetable area was a list of carotenoid rich fruits and vegetables. Those were highlighted. So HHS recognized the benefits of the fiber and the folic acid and all that, but it was very clear that carotenoids was one of the benefits that, one of the potentially beneficial nutrients that they were talking about.

With the American Cancer Society--oh, Tim, why don't you? Do you know it by heart? Because I--

DR. COLDITZ: You were on the committee that wrote the last guidelines; right?

DR. BYERS: Yes. Tim Byers. I did cochair that committee and wrote much of it. And I think the spirit of

the American Cancer Society guidelines for lowering cancer risk is really the same as for the HHS guidelines. That is that the best evidence is that fruits and vegetables lower our risk especially carotene containing fruits and vegetables, and the language in there, much like the language in the dietary guidelines for Americans, states that we don't know what molecules or compounds or nutrients in combination are accountable for that.

DR. JACOBSON: Well, I think it said anti-oxidant nutrients including carotenoids are thought to protect against cancer. We could obviously verify that.

DR. BYERS: I'm speaking more to the spirit of what the message is rather than the exact language, yes.

CHAIRMAN BRANDT: Okay. Well, I appreciate that clarification because--okay. Now open for discussion. No, no, not now. We're now open for discussion, please. Committee. Anybody have questions? Ms. Richardson.

AUDIENCE PARTICIPANT: If you're discussing the dietary guidelines, I have a copy.

CHAIRMAN BRANDT: Okay. Great. Can I have it, please? Can I borrow it?

AUDIENCE PARTICIPANT: I was on the committee. Could I comment on it?

CHAIRMAN BRANDT: No. We're now in committee discussion, but I appreciate your supplying a copy of the

guidelines. Okay. Thank you. Go ahead, Ms. Richardson.

MS. RICHARDSON: Yes. Mr. Jacobson, I was interested in the recitation about the 50 year old, possibly menopausal woman, who had to have her hormone replacement therapy changed and the question being was the absorption affected by her ingestion of olestra. Among all the reports that you've received regarding problems with olestra, do you have them categorized by age so that you would be able to identify menopausal/post-menopausal women?

DR. JACOBSON: Yes.

MS. RICHARDSON: Are there any other complaints regarding interference with HRT therapy?

DR. JACOBSON: No, that's the only one I recall. We had one other--we had a report of a hyperactive women who was on Ritalin, and she thought that olestra interfered with the absorption of Ritalin, and we haven't looked into that any further. It's a rather recent report.

MS. RICHARDSON: Well, working with older women, I guess I'm very interested in this issue with regards to the hormone replacement therapy. I do know that a lot of 50 year old women may be on Premarin, but they not be post-menopausal yet, and oftentimes do have to have their hormone therapy changed, the modes of administration as well. With so many of the baby boomers entering menopause and being concerned about their weight and possibly eating olestra, I

think that I'd like to see some more information about the possible interference with the absorption of hormone therapy, and certainly since the Women's Health Initiative is the largest, most comprehensive study being done on post-menopausal women, 26,000 of whom are in a hormone replacement trial, and another 40,000 who are in a dietary modification program, perhaps someone may want to follow-up with HHS to look at whether or not that question can be incorporated within the Women's Health Initiative?

DR. ZORICH: Dr. Richardson, there is data--

CHAIRMAN BRANDT: Wait. Peace. Dr. Askew.

DR. ASKEW: Dr. Colditz, you and your associates from Harvard have made some pretty dramatic predictions on mortality rates for cancer with some assumptions as to the effect of olestra on carotenoid levels. Did you see any reason to revise those estimates based upon the data that was just presented, the one-year to post-market survey in the Indianapolis area?

DR. COLDITZ: Well, the crux of the issue is whether market penetration is going to be as low as we're seeing in Indianapolis where we've got 26 people out of 700 or 600 in the high intake group. If that is the maximum market penetration nationwide, at that low level, then clearly we will have overpredicted. If marketing dollars are spent and penetration is higher, as was expected in the

original submissions, and that's where we started from to put this number together, then ten percent reduction in carotenoids is reasonable. But it really is driven by the market penetration and the frequency of consumption.

CHAIRMAN BRANDT: Dr. Byers.

DR. BYERS: The differences in finding in the epidemiologic studies, both blood based and dietary based, versus the trials is what I want to focus on. One possibility that maybe makes these not inconsistent but rather consistent would be that giving synthetic beta carotene alone and increasing by tenfold levels in the body might interfere in some way with lipid soluble nutrients also contained in fruits and vegetables whether those are carotenoids or others. I'd be interested in your comment on that possibility and perhaps Dr. Omenn's comment as well, if it's appropriate at this time? Is it possible or feasible that high dose beta carotene in the trials may be interfering in some way with an anti-cancer effect of lipid soluble nutrients contained in fruits and vegetables?

DR. COLDITZ: You're absolutely correct to raise that as one of the possible explanations for the results of the trials. There have been now several papers in the American Journal of Clinical Nutrition looking at the other carotenoids within participants in the trials, and the sense is both in the ones we've heard of today and some of the

other trials that have included beta carotene, the level of other fat soluble vitamins is not depressed as far as we can see. So that doesn't hold for me at the moment as the most likely explanation.

I suppose one of the real questions I have is the time frame when are the carotenoids acting in the pathway to cancer? Data I presented from our own analysis of lung cancer at the American Thoracic Society, but I don't have an abstract so I didn't present it, basically showed that diet in 1980, excluding 10,000 women who had changed their carrot consumption between 1970 and 1980, either increased or decreased, substantially strengthened the relation we saw between carrot consumption and decreased risk of lung cancer, which makes me think that we're talking about a relatively long-term effect since we were analyzing 1980 diet data and looking at lung cancer incidence through 1992, over some 12 years. Tightening up that intake from 1970 to 1980 strengthened our relations. So we had over a 70 percent reduction in risk in women with higher carrot consumption.

Now that doesn't say which carotenoid it is, but alpha-carotene is the only major source in humans is carrots. And whereas beta carotene comes from some 15 or so different food sources. But my point is that where we're acting in the time course to carcinogenesis is key and if

we've got to go and do randomized trials on 599 other carotenoids to fill in the gap from beta carotene to all carotenoids, it will be our great-grandchildren who get the benefits from the data.

CHAIRMAN BRANDT: Okay. Dr. Hubbard.

DR. HUBBARD: Graham, on your theoretical prediction for the future, did you try to model in the co-consumption of I mean the olestra containing products with the intake of the carotenoid containing products?

DR. COLDITZ: The assumption in that set of numbers is that some 80 percent of the olestra products are consumed around meals. Now, again the data we saw this afternoon don't quite support that. The 80 percent number was the one that Procter & Gamble had proposed to us through their initial submissions to the FDA.

DR. HUBBARD: And out of curiosity in a more generic sense, do you have any information on co-consumption with other fat-free products?

DR. COLDITZ: I certainly don't.

CHAIRMAN BRANDT: Other comments? Questions? Oh, boy, all of a sudden, hands went up everywhere. Okay. Dr. Feinleib, we'll let you go first and then Dr. Blaner.

MR. FEINLEIB: Thank you. Following up on these mortality projections, a lot of other things are going on currently with smoking, diet, exercise, et cetera. So I'd

like to ask Dr. Colditz, could you make a projection of what might be the first detectable sign of an adverse effect or fulfillment of your predictions if the current policy were maintained?

CHAIRMAN BRANDT: Which current policy are we talking about?

MR. FEINLEIB: I'm sorry. The current--

CHAIRMAN BRANDT: The current approval of olestra?

MR. FEINLEIB: The current approval of olestra, right. Yes, thank you.

CHAIRMAN BRANDT: Thank you.

DR. COLDITZ: That's a really important question, and as I look at the temporal relation between the carotenoids and endpoints, my sense is that the prostate cancer probably is the most proximal if we believe the blood studies. That the lung cancer, breast cancer, and other cancers may be further removed. So maybe we'd see a kick-up in prostate cancer first, but--

MR. FEINLEIB: And what would be the time frame on that?

DR. COLDITZ: If I had to make a guess, I'd say five to seven years, you should see an increase.

DR. JACOBSON: That's assuming heavy market penetration of olestra.

DR. COLDITZ: With the ten percent reduction.

DR. JACOBSON: Which I think is based possibly on about 30 percent of snack foods, savory snacks containing olestra. As I understand it, in Indianapolis, olestra containing snack foods, olestra containing potato chips comprise only three or four percent of the market, and olestra containing tortilla chips I think are under one percent. And those are the figures as to why it's hard for those various studies in Indianapolis to get many people with large intakes of olestra.

CHAIRMAN BRANDT: Dr. Blaner.

DR. BLANER: Question about Dr. Colditz--your comment about the other 599 carotenoids, does that mean this issue should not rest until all 599 have been examined?

DR. COLDITZ: No. I don't want to go that far, but I'm trying to contrast it with sort of extreme focus that's been placed on beta carotene in large part because of it's pro-vitamin A activity that got added to a review article, got lots of visibility, and spawned a series of randomized trials, and it was a gamble, and there are a series of at least four or five other clearly potentially visible biologically active carotenoids that now may be thought to be more realistic, but there are other carotenoids that we're either not measuring because we haven't got the food database together for all of them yet, or we don't have the analytic techniques together to really

know what their physiologic effects are.

DR. BLANER: Could I ask a second question? Could you provide me with some insight? One of the things that always confuses me about the epidemiologic evidence, especially the observational studies, that this carotenoid lycopene will be protective for prostate cancer, lutein will be protective for this cancer, and there seems to be this biological basis for this seems to be obscure. It's hard for me to understand how one is effective here, another is effective there. So how do you see that happening biologically?

DR. COLDITZ: The prostate actually, prostate and testes have very high concentrations of lycopene. Autopsy studies have been done and prostates have been ground up and HPLCed, and they've got high concentrations of lycopene. The retina has a different carotenoid from the lens. The question Tim asked early on about was beta carotene flooding out other carotenoids, in some sense that can be motivated by the sorts of analyses that Regina Ziegler did and Le Marchand in Hawaii did, where those with low levels of several of the specific carotenoids seemed to have the highest risk of lung cancer. So maybe the lung, there is more than one carotenoid important. We don't understand the cellular level of functioning of each of these agents, but the fact that you have prostate, testes and semen have high

concentrations of lycopene but other organs don't is at least plausible that there is some reason that it's there.

CHAIRMAN BRANDT: Okay. Dr. Benedict.

DR. BENEDICT: We have data--this concentration is an artifact.

CHAIRMAN BRANDT: Hold on. Hold on. Hold on. Dr. Benedict.

DR. BENEDICT: Two questions. The first is--and I apologize if somewhere this eluded me today, but do your predictions and your discussion of the various carotenoids that we haven't considered heavily, do they include a consideration of differential solubility in olestra? And does that exist?

DR. COLDITZ: Well, the data that Procter & Gamble submitted showed that different carotenoids came down at different levels, say with the 28 grams of olestra per day. We based our numbers on the total carotenoid reduction rather than in essence fiddling with each of them, but it suggests that different carotenoids will be influenced differently if the feeding study data hold up.

DR. BENEDICT: Yes. And so the differential you might have, in fact, over or underestimated specific tumors, give or take? It's not totally relevant. It's just a question.

DR. COLDITZ: Right. There's a lot of assumptions

underneath this, but you're right, yes.

DR. JACOBSON: Absolutely.

DR. BENEDICT: So, Dr. Jacobson, I'm sorry that hives have reared their ugly head yet again. You, of course, heard me ask Dr. Zorich about hives, and she said she had seen no hives nor heard of any hives, yet you report that they have. Can you reconcile this?

DR. JACOBSON: I can't. We get their reports from the FDA and we look through them and we find reports of hives and similar kinds of allergic like reactions. I don't know. Maybe one of P&G's committees that has looked at every one of the reports, Dr. Sandler's committee would have seen them, but I mean they're clearly there.

DR. BENEDICT: Thank you.

CHAIRMAN BRANDT: Okay. Any more questions of CSPI? Go ahead, Dr. Wang?

DR. WANG: Just a follow up, what you have observed, did the hives occur for a short-term, limited time, or it dragged on for a certain longer period of time, from your complaint you received?

DR. JACOBSON: We have graphed out how long the duration was.

CHAIRMAN BRANDT: Okay. All right. Now, several of you have questions of Dr. Omenn and others. Dr. Byers, would you like to ask your question of Dr. Omenn, who is

still here, I think?

DR. BYERS: Yeah. Just to repeat it, is it possible that the adverse effect of the beta carotene given in high dose in your trial as well as in the ATBC study, that that adverse effect might have been seen because of an interference with not necessarily absorption but with functioning of other fat soluble nutrients containing fruits and vegetables?

DR. OMENN: Certainly, Tim. That's a hypothesis worth investigating. It's been looked at, as Graham said, in several studies. There is no evidence that these doses of beta carotene, in the case of Finland, beta carotene plus E, in the case of CARET, beta carotene plus A, actually reduced any other carotenoids significantly.

There was a report from Arizona that the vitamin E levels were markedly reduced in young volunteer subjects, but there are now half a dozen studies, much larger numbers showing that somehow that was a spurious finding. And there is a lot of evidence given to spurious findings in these fields, it seems.

DR. BYERS: Let me follow up because that really wasn't the question I asked. I understand about blood levels and evidence that there is no substantial effect on absorption. Is it possible, however, that high dose beta carotene in these two trials might have interfered with the

functioning of fat-soluble nutrients contained in fruits and vegetables?

DR. OMENN: It's conceivable. I said that in the first sentence, Tim. The question is is it dose related? We looked and in Finland study they looked to see if the excess of the cancers and the excess of the heart disease deaths were in those people who had the higher blood levels within the range that was detected, and there was no difference by tertile of blood level on active treatment. So I mean it is hypothetical possibility that it starts with the presumption that the other compounds are, in fact, protective for which there is no direct evidence, only associations, and then it postulates a change for which there is no direct evidence, but it is certainly worth investigating as I said.

CHAIRMAN BRANDT: Okay. Dr. Zorich said something about in response to Ms. Richardson's question. Do you want to come to a microphone and respond?

DR. ZORICH: [Slide.] Yes. There were actually several trials conducted to look at estrogen, and there were two specifically in human and then one in rat. The two in human looked at typical serving sizes, and the rat then on an allometric scale was the equivalent of a much larger amount, about ten ounces of chips equivalent, if you would consider the dose given the rat compared to a human.

And what we found was, in fact, a no effect on the absorption of estrogen in either the human studies and, in fact, I'll show you the data from the single dose pharmacokinetic study, if anything the absorption was actually slightly higher on olestra compared to the full-fat or the water placebo. So there was no evidence of any effect on impaired estrogen absorption.

MS. RICHARDSON: What was the age range for the women in that study?

DR. ZORICH: This particular study was an oral contraceptive study, so they were women who were not postmenopausal. But the estrogen, in fact, is very similar in terms of its, how lipid loving it is between this type of estrogen and the active estrogens in Premarin.

CHAIRMAN BRANDT: Okay. Are there any other questions about this issue?

DR. CHASSY: Is it possible to ask Professor Sudi what it was that he wanted to say?

CHAIRMAN BRANDT: It is possible for you to do that, yes.

DR. CHASSY: Bruce Chassy is asking Professor Sudi to share with us what he thought the committee intended in the guidelines.

CHAIRMAN BRANDT: Okay. That's fine. Go ahead, sir.

DR. SUDI: Yes, I was on the dietary guidelines committee. I guess I don't remember any discussion to the effect that we were trying to make a statement specifically indicating intake of carotenoids as being all that important. And I gave you the copy. The wording referring to carotenoids under the section eat more fruits and vegetables, and it indicates a couple of things. It indicates that fruits and vegetables have a number of things in them including carotenoids which are including carotene, a precursor of vitamin A, and then it references a table that was referred to, and pointing it out mainly as a precursor rather than as any other effect, and on the next page it also has a table of folate content of different foods. So that was dealing more with the vitamin content.

And then there is a statement that says, I think it says many, some scientists, or there is interest amongst the scientific community about the possible effects, positive effects of carotenoids as anti-oxidants, and it leaves it go at that. So I think and similar to what Dr. Byers said that the statement of that committee was directed really towards telling the public eat more fruits and vegetables.

CHAIRMAN BRANDT: I'll read it to you exactly. The anti-oxidant nutrients found in plant foods, and it lists them, vitamin C, carotenoids, vitamin E and certain

minerals, are presently of great interest to scientists and the public because of their potentially beneficial role in reducing the risk for cancer and certain other chronic diseases. That's an exact quote from this, assuming this is a legal copy of--

[Laughter.]

CHAIRMAN BRANDT: That's an exact quote and you can have it back. Anybody else on the committee--we're strictly at the committee--have any questions about this issue? Dr. Feinleib?

MR. FEINLEIB: With regard to the second item in our charge to evaluate the results of active surveillance, will we be getting any written material or documentation in the next 24 hours?

CHAIRMAN BRANDT: No. You've got all you need. That's why you've been here.

MR. FEINLEIB: Not all I want but all I need.

CHAIRMAN BRANDT: Well, all you need may not be all you want, but it's all you need. Okay. Dr. Blaner.

DR. BLANER: Could I have the follow-up from P&G on the question I asked Dr. Colditz?

CHAIRMAN BRANDT: You may indeed.

DR. TREIBWASSER: This is the question regarding the distribution of cancers?

CHAIRMAN BRANDT: You all got to identify

yourselves or you're going to drive our recorder nuts.

DR. TREIBWASSER: Keith Treibwasser, Procter & Gamble. We do have one specific piece of data that we would like to share on the lycopene distribution, and then we would also like to comment on some of Dr. Colditz's comments on our executive summary. So we will share the lycopene data first.

[Slide presentation.]

DR. PETERS: Actually, as Dr. Colditz mentioned, when the first Giovannucci finding was published, there was some interest in the notion that lycopene may be quote "concentrated by the prostate gland." And there have actually been papers that have been published in the last several years which look at the tissue distribution, and Steve Clinton has published a review which indicates the prostate lycopene concentration, a mean of .8 nanomoles per gram, and if you look at the distribution across the different tissues that contain lycopene, clearly the prostate is one of them that contains lycopene, as I mentioned. Liver has a higher concentration. The adrenals have a higher concentration in addition to the testes that he mentioned, and this is true in all the studies that have looked at. So I just wanted to point out that there is no special selection by the prostate to take up lycopene. It tends to mirror the rank order of carotenoids that are found

in the blood, which in turn mirror the rank order of carotenoids that are found in foods.

So while the different tissues may have different absolute levels, they all tend to be rank ordered in the same pattern occurring in blood and food for the most part. Just a couple of other comments. I should mention the executive summary is just that, it's a summary. We provided the more detailed information--

CHAIRMAN BRANDT: Wait a minute. Let's be sure he's got an answer to his question. Okay.

DR. BLANER: That's sufficient.

CHAIRMAN BRANDT: Thank you, sir.

DR. PETERS: And we did not cite abstracts that have not yet been peer reviewed. We stuck with the peer reviewed literature and that's what's contained in the comprehensive literature review that you have. And then I don't know if I really wanted to get into the game I suppose of selective citation as it were, but I have a couple of overheads that may be worth sharing with the committee.

CHAIRMAN BRANDT: About what?

DR. TREIBWASSER: Well, these are particularly relevant since Dr. Colditz cited both Dr. Regina Ziegler of the NCI and Dr. Mares Stampfer of Harvard in his comments, and we would just like to share a couple of quotes from those two authors that bear on this question.

[Slide.]

CHAIRMAN BRANDT: Okay. First, assume that we can read so you don't have to read it to us.

[Laughter.]

CHAIRMAN BRANDT: Assume we can't read it that small.

DR. PETERS: Thank you.

CHAIRMAN BRANDT: This has not been my day. Okay.

[Laughter.]

DR. PETERS: I apologize for the mouse type so perhaps I will read the bottom.

CHAIRMAN BRANDT: It's a good thing we have all these ophthalmologists here. That's all I can say.

DR. PETERS: This is a review that Dr. Regina Ziegler wrote with Susan Taylor Mayne and Christine Swanson. And I just want to point out that the review was on factors relating to lung cancer which included carotenoids among other things. They cited that the evidence is certainly--there is the most information available about beta carotene, but the totality of evidence, epidemiologic evidence is not at present persuasive for anyone of these micronutrients, and they included carotenoids as well as things like vitamin C, E and selenium, and that was published in 1996.

Then I just wanted to mention one other quote that Dr. Stampfer has made in one of his own publications

evaluating the strength of the evidence about cardiovascular disease risk and carotenoids, and I will admit the emphasis in his own paper was on beta carotene, but he suggested that the inverse association between beta carotene and coronary heart disease from observational studies is most plausibly explained by other dietary components found in fruits and vegetables with high beta carotene concentrations.

So I think if you take any of these papers and go searching around for snippets, it's possible to find things. Even people such as have been mentioned here, who have opinions about this product, when they perhaps wear their scientific hats, they've made statements that are, well, I've--

CHAIRMAN BRANDT: Okay. We read them. Okay. Any other comments? Hearing none, we will take a 15 minute break. That means reassemble at five after four.

[Whereupon, a short break was taken.]

CHAIRMAN BRANDT: It's time for us to come back to attention, as it were. So we're ready to go. Hey, hey, everybody. All the talk, please--okay. We're back to Dr. Larsen who's got some kind of announcement or something.

DR. LARSEN: Coming around at your places are three pieces of paper that have been talked about earlier this afternoon. You already have in your folder a letter from Robert Talbert. That was given to you earlier in the

meeting I think first thing yesterday. What Dr. Jacobson has advised is that you should take the one that is coming around now and replace it because this is the revised version.

The second piece of paper, the last page is the material that Dr. Brown cited yesterday from the petition to FDA and that's that last page, and the first couple of pages apparently are something he's done on analyzing that data.

The third piece of paper is the remarks provided by Gil Omenn he said that had been passed out beforehand. But we didn't have enough copies. We do now, and you're getting it now.

CHAIRMAN BRANDT: Okay. I'm going to read into the record a letter from somebody who couldn't be here to testify during the public. It is from the Honorable Julia Carson, member of Congress. Dear members of the Food Advisory Committee: Although I am unable to personally appear, I request that my concerns about olestra be a part of your official record. Indianapolis, the congressional district I represent, served as a test market for snack chips which contain olestra. Soon after these products were in the market, I began to receive a preponderance of complaints about them, complaints that I had never received on any other food product.

Consumers were complaining that snack chips with

olestra had caused them to experience abdominal cramping and diarrhea, frequently severe enough to result in the need for medical attention. Products with olestra are now available on the national market and the FDA has received more complaints about these products than any other item they have ever approved. Obviously there are problems with olestra. The adverse effects of olestra are thoroughly documented. Procter & Gamble has sponsored research that would refute the harm caused by this product. Philip Morris once sponsored research that also refuted harm only then the product was cigarettes.

I would contend that research sponsored by those with a vested self-interest is not the objective research that is required when dealing with the health of the nation. There are still too many unanswered questions about olestra. In this obesity laden nation that we live in, the lure of a fat-free snack chip is enticing to adult consumers. Children are attracted to the colorful package and exciting name, "Wow." However, the potential risk could be devastating. Given the unanswered questions and the known physical side effects of olestra, perhaps we should not be asking could we consume this product but should we consume this product? I would contend that we should not. I urge the FDA to carefully review olestra and require that the product warning label be prominently displayed both on the

actual food item and on the grocery shelf.

The FDA needs to ensure that consumers have the information to make an educated choice on whether to consume products which contain olestra. Sincerely, Julia Carson, Member of Congress. So that's been read into the record. Okay. Moving on to our colleagues from the FDA. What?

DR. LAMM: May we respond to this letter?

CHAIRMAN BRANDT: No. Not any more than we respond to anybody on the public hearing. So she had originally intended to be here to give this testimony in person, couldn't, so she sent a letter. So that's it. It does become part of the record like everybody else's, and like these dozens of letters that you've gotten. If you want a copy of it, you can have it, I presume. I don't know of any reason why not.

Okay. The FDA--are you all ready? Hello, FDA. Okay. You have 45 minutes and we're starting off with Dr. John Vanderveen.

DR. VANDERVEEN: That's correct.

CHAIRMAN BRANDT: Okay. Emeritus research scientist and consultant. Okay, sir. Fire.

DR. VANDERVEEN: Fine. Go ahead and put the slide up.

[Slide presentation.]

DR. VANDERVEEN: The carotenoid issues raised

during the rulemaking on olestra are shown on the slide there. I'm only going to cover the carotenoid issue and we'll have some other discussions by other people. Carotenoids when consumed in the same eating occasion will be partitioned into olestra resulting in decreased absorption, as evidenced at that time. Decreased absorption of carotenoids will result in depletion of tissue stores were evident. Decreased tissue stores of carotenoids were hypothesized to increase the risk of certain forms of cancer, cardiovascular disease, macular degeneration. Those were the issues that were raised during rulemaking.

Next slide, please. Let me go through the hypotheses that were raised during rulemaking and then respond to what has happened since 1996. The first one is beta carotene lowers the risk of lung cancer based on observations that diets high in fruit and vegetables, which also contain beta carotene show a protective effect on lung cancer.

Next slide, please. You've heard the hypothesis that based on retrospective study, lycopene tissues stores can lower the risk of prostate cancer. The next hypothesis: carotenoids in oral cancer. Carotenoids lower the risk of oral cavity cancers based on observations that diets containing high amounts of fresh fruits and vegetables have been associated with lower levels of oral cancer.

Next. Carotenoids lower the risk of breast cancer based on observation that diets contain higher amounts of fruits and vegetables have been associated with lower breast cancer risk. Next slide. Carotenoids and cardiovascular disease--carotenoids lower the risk of cardiovascular disease based on the observation that carotenoids under certain conditions can act as antioxidants and thus could protect against oxidation of low density lipoproteins.

The hypothesis that lutein and zeaxanthin and the macular degeneration. Both lutein and zeaxanthin as you heard today are in the eye, lower the risk of macular degeneration based on the observation that both of these carotenoids are found in the macular region of the eye, and that their antioxidant properties might protect against light irradiation. We've heard a lot about that. I don't plan to discuss that anymore today, but that was one of the issues that was raised as well.

Now, FDA's findings in the 1996 document that we published on, the final document on olestra, beta carotene and to a lesser extent alpha carotene and beta cryptoxanthin can be converted to vitamin A. Our second finding was FDA indicated there was not direct evidence that the association between the consumption of diets rich in fruits and vegetables and a decreased risk of cancer was due to carotenoids themselves.

The scientific developments of the last two years, I'd like to say that we have looked at the literature. There have been several hundred scientific papers that have been published on the association of carotenoids and degenerative diseases. We put more emphasis on intervention trials. We did look, however, at the peer reviewed literature. That included observational studies and including both--and also cohort studies and that is the data that we have looked at. We also looked at experimental research in animals and also information of tissue studies as well.

Now, we also paid attention this time around, even though we did have the information from Dr. Willett or the publication that he has of his conference that was organized in the late 1996 time frame on the effects of olestra and the impact on carotenoid absorption, the potential decrements and benefits. We were aware of that information. We had an observer at that meeting, and that was taken into account with our final regulation, and we did again take a look at what was indicated in that document.

Next slide, please. Significant note was looked at some of the major studies that were published since the January 1996, and this is the second major prospective study, the CARET study which you have heard a great deal about today. And this study as indicated by the author had

significant lack of beneficial effects of beta carotene in both lung cancer and heart disease.

The next slide, please. But to say that it's quite evident, looking at the literature, several new epidemiological studies support the observation that diets with increased levels of fruit and vegetables lower the risk of cancer, cardiovascular disease. However, none of these new studies provide any direct evidence that carotenoids are in themselves responsible for these observations.

May I have the next slide, please? To say that several studies have been published on the relationship of beta carotene intake and on blood levels with the development of head and neck cancers, in particular one group of studies show a regression of premalignant lesions, and one small study in which vitamin A and beta carotene were compared, vitamin A was more effective than beta carotene indicating that the effect may be due to conversion of beta carotene to vitamin A, and there is some other data to indicate that this conversion does occur at various tissue sights within the body. So it's not inconceivable. Most of these studies come from areas of the world where vitamin A status was quite poor, and there is reason to believe that perhaps the population may have been vitamin A deficient.

So those are the major observations that we were

able to look at relative to the literature. Now, conclusions. It's my conclusion at this time that a review of the literature published since 1996 finds that there is still not direct evidence that the association between the consumption of diets rich in fruits and vegetables and a decreased risk of cancer was due to any single or group of carotenoids in themselves.

Secondly, studies published since 1996 do not support the hypothesis that lycopene reduces the risk of prostate cancer. I did not look at, however, any abstracts, research that deals with abstracts in this area. Conclusion: there is no data published since 1996 that provides direct evidence that beta carotene protects against the oxidation of low density lipoproteins in the body. In fact, I find in reading the literature that there seems to be a general lack of support for that hypothesis. Direct observations of the CARET study show no benefit from beta carotene supplementation. And that's a summary of our review of the literature at this point in time, of the literature I want to say that was published since our review, our publication of the final olestra document. Thank you.

CHAIRMAN BRANDT: Thank you very much, Dr. Vanderveen. By the way, Dr. Vanderveen just retired on June 3, I'm told, so I'm only two weeks late in calling you an

emeritus. Dr. Thomas Wilcox.

DR. WILCOX: See if I have better luck with the pointer today. Ah, there we go.

[Slide presentation.]

DR. WILCOX: I'm going to briefly discuss the olestra post-marketing surveillance study findings from the first year at the sentinel site that Procter & Gamble folks talked about at length a little earlier. We just got this data recently so I've essentially just reviewed their written report and haven't had time to delve into the data in depth. So we'll spare you all the graphs and the numbers that we did during the home study.

Now, this is a really nicely designed project. We have the random digit dialing for dietary details. What did they eat and when did they eat it? Some very interesting results with that, and then the cross-sectional study to see population as it exists in Indianapolis, what was the effect, if any, of olestra in that population during the first year of its distribution there. And then the clinic cohort study, they had hoped to get a cohort of people who were heavy olestra consumers and follow them over time to see what effect olestra ingestion might have on their nutritional status.

Next slide. This is from the random digit dialing. They found that there was no change in fruit or

vegetable consumption as they had mentioned. They also found that 96 percent of the people in Indianapolis would eat savory snacks at least once per month. That's essentially almost everyone in the population. They also found that the median consumer ate 13 savory snacks a month. That's sort of a higher consumption than I would have expected so it's clear that savory snacks are popular in the population. And the data I found most interesting was the co-consumption of savory snacks and fruits and vegetables are rare. Now this is savory snacks. This is information that they obtained in year zero to see how often they would eat potato chips or corn chips or whatever with their meals.

And about 12 percent of the time at lunch or at snack, they would be co-consuming, eight percent at dinner, and .4 percent at breakfast. So some people their savory snacks around the clock apparently. Now, the figure that is most interesting to me, and they mentioned it earlier, about 14 percent of total carotenoids are consumed at the same time as savory snacks. So if you look at, they eat about 13 savory snacks a month, and they co-consume about 14 percent of the time the total carotenoids. I guess I would estimate that each time they eat a savory snack they eat it with one percent of their carotenoid intake for the month.

So that if someone were to eat all olestra savory snacks and eat their 13 olestra savory snacks per month,

they would co-consume with about 14 percent of their carotenoid intake for that month. Now in theory, that would decrease, at most decrease their carotenoids level by about 14 percent assuming that it was all sequestered in the olestra and exited the GI tract without absorption.

Now, if you assume that they just ate one olestra savory snack a month along with their 12 other non-olestra savory snacks, that would imply they would co-consume with one percent of their carotenoid intake for the month. So that's the average intake in their clinical cross-section. They eat it about once a month. So in theory at least one would expect their carotenoid level would not change by more than a percent.

Next slide. Just to talk about the clinical cross-section results, as they mentioned earlier, there was no statistically significant decreases in population weighted means, serum carotenoid or fat soluble vitamin concentrations. No significant associations between olestra intake and total or specific serum carotenoids. Those are findings that are not surprising considering the level of intake in the clinical cross section population. They did find some benefits--decreased energy intake from fat. It went from about 34 percent with the non-olestra consumers to about 30 percent in the people that ate at the highest consumption levels. Also, a positive trend for serum

vitamin K increasing with increasing olestra ingestion. It essentially went up 20 or 25 percent from the lowest, from the non-olestra consumers to the highest level of olestra consumption.

Next slide. In the clinic cohort results, now the clinic cohort, these are the people that were recruited to try and get as heavy olestra consumption as possible. There were statistically significant decreases between year zero and year one in total carotenoids, lutein, lycopene, zeaxanthin, retinol, and 25-OH vitamin D. There was a statistically significant increase in beta cryptoxanthin, and none of these changes had any association with olestra ingestion. It apparently was just a random variation. There was no ready explanation that can determine at this point. Considering how variable the carotenoid levels in blood can be, this type of occurrence was not unexpected or not surprising.

Now, in the heavy eater cohort, even in this selected cohort, only 35 percent of the participants reported eating any olestra in the previous month. Just to talk about vitamin K again, the trend for vitamin K to increase with increased olestra ingestion did not quite reach statistical significance. It was p .06, but there seems to be a fairly clear trend here. Next slide.

I'd just like to talk about olestra intake in the

studies at this point. Once again, the savory snack consumption is fairly common in the population, 13 times a month. The year one cross-section, the median frequency of consumption was .9 times per month. 90th percentile was 64 grams per month, which is about eight ounces of chips per month. In the cohort, clinic cohort, 35 percent in the last month. There the median consumption only went up to 11.9 grams per month, and the median frequency is still around once per month. So here, as we discussed earlier, even for the clinic cohort, you're not going to expect to see, you know, if the theories are correct, much more than a percent difference effect on the carotenoid levels from the levels of ingestion that we have participating in the study at this point.

And again, earlier I think some people on the committee were talking about the numbers of high consumers that we have in these studies at this point. There were 26 people, greater than two grams a day. This is 20 in the cohort. This is really, there are very few people to study over the three or four year length of the project here. Hopefully, when they get the other centers to participate, we'll have increased numbers in these higher consuming cohorts. Can I have the last slide, please?

Okay. Conclusions. The olestra consumption in the population is low at the present time. The carotenoid

decrease from year zero to year one in the clinic cohort does not appear to be associated with olestra ingestion. Vitamin K increase possibly associated with olestra ingestion needs some post-observation with regards to the proper level of supplementation in the olestra with vitamin K. And the last, the data from additional study centers will be most helpful in evaluating the olestra nutritional issues, especially if we can get participants in the clinic cohort that have higher consumption than we have at present. Thank you. Now, Dr. Alan Rulis will present the concluding remarks.

DR. RULIS: I don't see the chairman but--

DR. LARSEN: He stepped out a moment.

DR. RULIS: He stepped out. Well, I'll say what I have to say anyway. Actually I don't wish to add anything at this time. I think we'd be more interested in entertaining the committee's questions of our FDA group and then also getting right into the committee discussion and hearing that. So--

DR. LARSEN: On that, until Dr. Brandt gets back, I will just try to keep track and go on and let you ask your questions. Dr. Harlander, first.

DR. HARLANDER: Is it FDA's opinion that the amount of vitamin K that is added back to olestra needs to be reevaluated or just monitored over time? Do you feel

it's been oversupplemented at this point based on the results that we have to date?

DR. RULIS: I'll start. I'll let John Vanderveen and Dr. Wilcox add if they have anything to add to it, but I think at this point I don't think we have anything concrete to say on that matter. I think we've addressed the question in the rule, in the approval rule, adequately, but it always bears looking at, and if the new data raise a question or a concern, then I think we have to pay attention to it, but at this point, I think it's premature to make any judgments. Dr. Vanderveen, do you have any--

DR. VANDERVEEN: If you don't mind, I just might mention that of the four fat soluble vitamins when we were in the process of looking at the data and agreeing to what the supplementation rate should be, we did not have the base of information for vitamin K that we have for the other three vitamins primarily because it was not possible at the time to do the same type of studies to develop that base without running the risk of serious problems in the experimental study, and so as a consequence, there was a rather conservative view put forth by FDA to see that there was adequate vitamin K in the product, and I think that's adequately explained in the Federal Register document.

DR. LARSEN: Dr. Benedict.

DR. BENEDICT: This is for Dr. Wilcox. And I'll

call upon my gastroenterological brethren to correct me if what I have to say is not right, but I appreciated your comparison of co-consumption and the percentages, and that was very helpful. If one assumes what I think to be the case, and that is that over a period of time, you have randomization in the sense that things aren't going to move through the colon or through the small intestine as a unit if one of them is an oil and the other one is a non-oil, would you modify your calculations if it turned out that things were going to randomize along? Would that decrease or increase the percentage drop significantly, in your opinion?

DR. WILCOX: I'm not the best person to ask that. What I understand about olestra is that if you co-consume within an hour or so, there's a good chance for sequestration. If it's beyond that time, I think there may be some but probably considerably less.

CHAIRMAN BRANDT: Dr. Lamm.

DR. LAMM: Dr. Wilcox, I was very impressed with your elegant summaries of the active surveillance program that was presented by the complex matter that I thought was presented very clearly by you, and I would appreciate if we might, you might be able to make available copies to us for us to review this evening copies of your overheads?

DR. WILCOX: Certainly.

DR. LAMM: My question to the FDA is that with the evidence being presented here on the vitamin A, is there under discussion within the EPA [sic] to reduce the level of vitamin A supp or fortification of the olestra?

DR. RULIS: Are you talking about vitamin A or K?

DR. LAMM: K. Sorry.

DR. RULIS: Right. K. Short answer is these data are very new. As you heard from Dr. Wilcox, we're not even at the point where we're doing really serious number crunching, and we don't have all the graphs as we would like. That is underway, and it will be ongoing for some time. Right now we're in the mode of listening to your opinions about this, and I think we will consider those, but we have to look at the data ourselves very carefully, and that we haven't done as much as we would like at this point in time.

CHAIRMAN BRANDT: Dr. Byers.

DR. BYERS: I just want to try to make sure I'm clear on something, and that is that eating of olestra in the test market in this pilot study with and without food, 14 percent figure, please explain that to me again?

DR. WILCOX: Well, that was the figure provided by Mark Thornquist and the folks from Hutchinson. But essentially as I understand it that if your median amount of consumption of savory snacks now, if you eat those 13 times

a month, on average you will consume 14 percent of your carotenoids at a time when you're eating a savory snack.

DR. BYERS: Okay. Of all of the olestra products eaten, however, most of them were eaten with other foods as I understand it, and perhaps this question should go to the--

DR. WILCOX: No, I'm talking about savory snacks. I'm not talking about olestra.

DR. BYERS: Well, okay. Savory snacks containing olestra.

DR. WILCOX: Well, no, these were savory snacks. This was before the introduction of olestra. This was any savory snack eaten at a meal where carotenoid containing vegetables or fruits were also consumed. What I'm saying is that the propensity to consume savory snacks with your meals would, I assume, be the same for olestra savory snack or more traditional savory snack. I'm just postulating that if you ate, if all of your 13 savory snacks for the month were olestra, you would absorb, you know, a considerable portion of the carotenoids contained in that meal that you were co-consuming.

DR. BYERS: But I'm just trying to resolve this with the data we heard earlier that, in fact, a minority of the savory snacks are eaten by themselves. So amongst people who eat savory snacks, those tend to be eaten with

other food; is that still correct?

DR. WILCOX: There the data presented said that at lunch or during a snack, 12 percent of the time you will eat a savory snack with a fruit or vegetable. For dinner, it's eight percent of the time. So in other words, potato chips at dinner are fairly rare, but eight percent of the time they may appear on the menu.

CHAIRMAN BRANDT: Okay. Dr. Clancy.

DR. CLANCY: Two questions. One of them really is to the Fred Hutchinson people, but maybe, Dr. Wilcox, you can answer this. Are we talking about eating occasions here or are we talking about meals? I'm being very confused.

DR. WILCOX: I think we better have the folks from Hutchinson describe this. They can do it better than I can, I'm sure.

DR. CLANCY: And I have a particular interest in eating outside of the home here, not at mealtime.

CHAIRMAN BRANDT: Okay. Can you answer that briefly, please?

DR. CLANCY: I have another question after that.

DR. KRISTAL: What I'd like to do is tell you that there's a baseline manuscript on these results that's been accepted for publication, and we're duplicating it right now, and when it comes down, I could read you some numbers, but we're making you all copies. And there are some

extensive tables that are clear about that result.

But, Tim, just to answer your question, if I may be allowed to clarify what that 14 percent is? Is that okay?

CHAIRMAN BRANDT: You may.

DR. KRISTAL: That number is that on average of the total amount of carotenoids consumed in a single day, 14 percent of those carotenoids are consumed within an hour one way or the other of eating a savory snack, any kind of savory snack, anytime during the day. That's what that 14 percent means. So it's sort of 14 percent of carotenoids are quote "at risk".

CHAIRMAN BRANDT: Okay. Dr. Clancy, you have another question?

DR. CLANCY: Yeah. I'd like to ask John Vanderveen, can you give an estimate of the somewhat over 200 studies that you've looked at that don't include abstracts, if you remove all of the studies that only focused on beta carotene and then you take that number of studies and you spread it across all possible disease conditions, many of which were mentioned by Dr. Colditz, approximately how many studies do we have aside from the beta carotene studies for each of these chronic disease conditions? I mean have we developed a definitive catalog of literature on the carotenoids as a whole across all these

disease conditions? Are we early on in the process of doing that? That's my question.

DR. VANDERVEEN: The majority of the literature clearly was associated beta carotene. However, there are other reports in the literature for other carotenoids or total carotenoids which is also prevalent. Where are we relative to the science of carotenoids? I think that we'll be studying carotenoids for a long time to come, but I think more importantly, it appears that we ought to be looking elsewhere for fresh fruits and vegetables to determine what might also be beneficial in terms of lowering the risk of cardiovascular disease in the various cancers that have been postulated as being important for fresh fruit and vegetable consumption. I think we have focused--I mean if you want an answer as to why the observations that fresh fruits and vegetables consumption is--consumption is correlated with reduced risk of those diseases, I think we have to look more broadly. And I'm not suggesting that there might not be some carotenoid interaction with other compounds as well, but at the present time, there's not definitive information that would pinpoint it as being carotenoids that are the valued component.

CHAIRMAN BRANDT: Dr. Clydesdale.

DR. CLYDESDALE: I have two questions. The first one, I thought, had been answered, and then a couple more

comments were made and I became more confused, but I might ask again, Dr. Wilcox, how many--this is Dr. Byers' question. So how many, what percentage of time are savory snacks eaten within an hour of meals?

MR. FEINLEIB: Could we see that overhead?

DR. CLYDESDALE: Tim, are you clear on this? Maybe you can help? Are you clear on this now?

DR. BYERS: Yeah. I think there is two different questions and yours really pertains to if somebody, of all the savory snacks consumed--

DR. CLYDESDALE: Yes.

DR. BYERS: --what proportion of them are consumed within an hour of eating other foods?

DR. CLYDESDALE: That's what I want to know.

DR. BYERS: Yeah, and that is a different figure than the 14 percent. What's the answer to that?

DR. CLYDESDALE: So is that the 20.4 percent?

DR. WILCOX: [Slide.] The data would indicate that 12 percent of the time at lunch or snack, you will consume a savory snack along with the lunch or the snack; eight percent of the time at dinner. Now, this other figure, this 14 percent figure, I think it might be best for the folks from Hutch to explain how that was arrived at. But my understanding is that all the carotenoids that you ingest, I guess think in terms of a month--think in terms of

a month--that 14 percent of those carotenoids will be ingested within an hour of having had a savory snack.

DR. CLYDESDALE: And is that based on eating savory snacks 20 percent of the time within an hour of meals?

DR. WILCOX: No. My understanding is it's based on eating 13 savory snacks a month.

DR. CLYDESDALE: Well, where is that--I guess those last two dots I'm getting confused on because there are two separate issues, and I guess I just wondered--

DR. WILCOX: I think it's best to of our friends from Hutch.

DR. CLYDESDALE: Yeah, okay.

DR. KRISTAL: May I? The first question about the co-consumption of savory snacks with fruits and vegetables, any minute now we will have a table that we're distributing to you. So I promise that to you. The second question about the 14 percent number, are you asking me where that came from?

DR. CLYDESDALE: No, I'm okay on that. I'm okay on that.

DR. KRISTAL: Oh, okay. Great. So the first question, I promise we will have tables distributed to you very soon about exactly what those data look like and where they're from.

CHAIRMAN BRANDT: Okay.

DR. CLYDESDALE: I have a second question if I might.

CHAIRMAN BRANDT: Go ahead, sir.

DR. CLYDESDALE: There has been a lot of discussion on the carotenoid absorption, and I'm going to have to go back to some data presented at the last meeting, Mr. Chairman. Sorry. I'm going to have to ask for that. Is that okay?

CHAIRMAN BRANDT: I reckon.

DR. CLYDESDALE: I guess with the lipophilic partition coefficient that was introduced, it was my understanding, and I can ask Dr. Vanderveen this, that beta carotene and lycopene were affected as premeasured by the lipophilic partition coefficient, and lutein and zeaxanthin were about 1000 times less affected. I wondered what--are the other carotenoids less affected like lutein and zeaxanthin or where do they fall in with the measurements in the lipophilic partition coefficient? Because that gives us some idea of the other carotenoids that were discussed earlier, how they would be affected, and I think that's very important.

DR. VANDERVEEN: I thought I could come up with the data real fast. You're right.

CHAIRMAN BRANDT: You got to be on the mike before

you say you're right.

DR. CLYDESDALE: No, no. He can say that any time.

[Laughter.]

CHAIRMAN BRANDT: Not if he wants it part of the record, he can't.

DR. CLYDESDALE: I don't get that much.

DR. VANDERVEEN: Yeah, you got to get it when you can get it.

DR. CLYDESDALE: Exactly.

CHAIRMAN BRANDT: But it ought to be on the record.

DR. VANDERVEEN: As I recall the figures, maybe somebody from P&G can correct me if I--I believe the factor is about 17 for the first group which included beta carotene, alpha carotene, and lycopene, and then it dropped hundred-fold for two of the others, and then another thousand-fold below the beta carotene for some of the other carotenoids, but you must also remember that you're dealing with many of these carotenoids. Beta carotene is so overwhelming in terms of the amount that's present and alpha carotene and cryptoxanthin are relatively significant, but when you start getting into the other carotenoids, you're dealing with something that is extraordinarily small in many foods. There are very low amounts in our food supply.

So not only are their partition coefficients much different but also the fact that they're there in very, very small amounts, and we know very little about it. I might mention one other issue, if I might. From perspective within the Department of Health and Human Services and discussions that I've been involved in over the last 15, 20 years, our discussion of always talking about carotenoid containing fresh fruits and vegetables had as much to do with color, which they are the source of the color in these, to help the public understand what you're looking for, as opposed to the fact that the content of carotene is an important component. Also as indicated, vitamin A was considered to be an important component of food and the carotenoids were there for the purpose--always considered to be important both from considerations that dietary consumption as well as other factors or further properties in vitamin A.

DR. CLYDESDALE: Thank you. Do you have that data? Did someone have those data on the partition coefficients.

CHAIRMAN BRANDT: What data? Oh.

DR. CLYDESDALE: I'd like--if it's not--I don't mean--

DR. PETERS: I have the data up here. We're looking for the slide. But what Dr. Vanderveen said was

essentially right. The top three lipophilic carotenoids are alpha, beta carotene and lycopene, basically the hydrocarbon carotenoids, and they run at about 17.6 to 18 on the log partition coefficient scale for--

DR. CLYDESDALE: And just help me. That corresponds to a level of malabsorption of what? A log of 17.6 corresponds--if the same meal was eaten to a loss in absorption of what?

DR. PETERS: In the controlled studies, if you co-consume olestra with those particular carotenoids, the effects are in the range of 50 to 60 percent reduction.

DR. CLYDESDALE: So that compares to about 17.6?

DR. PETERS: Right.

DR. CLYDESDALE: Okay.

DR. PETERS: Now the other xanthaphils, that's the other carotenoids, the ones that are hydrox-solular like lutein, zeaxanthin, beta-cryptoxanthin, are about a thousand times less lipophilic, and correspondingly, they are less affected under those controlled clinical conditions, somewhere between a half and a third as much of an effect on absorption.

DR. CLYDESDALE: Okay. Between a half and a third, and then the rest of the carotenoids are even less lipophilic even though they are there in small amounts?

DR. PETERS: Well, the carotenoid class, as Dr.

Colditz pointed out, has up to 500 compounds. They run all the way down to below six. The major ones in the diet are all probably between about 13-/1/2 and 18. So they're all in that range of the ones that we've been talking about.

DR. CLYDESDALE: Okay.

CHAIRMAN BRANDT: Okay. Dr. Bernstein.

DR. BERNSTEIN: For Dr. Vanderveen, was there a reason why you did not want to express an opinion on terms of carotenoids and macular degeneration?

DR. VANDERVEEN: Oh, I thought I implied that the data weren't there to draw any conclusions at this point in time. The fact that those carotenoids are found in the macular region of the eight is a fact that has been expressed here today. But we couldn't find in the literature any definitive data to indicate further their value to the whole process of macular degeneration with age, and it's a hypothesis at this time, and it's an open hypothesis at this time. There were, there is some interesting data about their presence, but the literature that we saw relative to this indicated that there was some new thoughts about light radiation and its impact. The Australian data seemed to indicate that the level of intensity of light had less to do with macular degeneration. If that is sustained, then you start questioning whether the real function was ionizing radiation as a factor in their

usefulness in the eye.

Perhaps they have some other function is yet not present, but at the time that we were going through the evaluation of the data back two years ago, that was the primary hypothesis put forth in the comments, that macular degeneration was, that carotenoids protected against light irradiation. If that's not the predominant theory at this point in time or there are some other theories, it's not evident yet.

CHAIRMAN BRANDT: Okay. Dr. Chassy.

DR. CHASSY: Fergus got my questions.

CHAIRMAN BRANDT: I'm sorry.

DR. CHASSY: Professor Clydesdale got my questions.

CHAIRMAN BRANDT: Oh, okay. So he done two things right today. Okay. Good.

[Laughter.]

CHAIRMAN BRANDT: He can't hardly beat that. Dr. Fukagawa.

DR. FUKAGAWA: Yes, Mr. Chairman. It is okay to ask Procter & Gamble what their estimate of the market share?

CHAIRMAN BRANDT: Not now.

DR. FUKAGAWA: Okay. Thank you.

CHAIRMAN BRANDT: Dr. Feinleib? This is strictly

FDA.

MR. FEINLEIB: It's essentially the same question, but I'll try to disguise it.

CHAIRMAN BRANDT: You can only ask the FDA questions about where they are in all of this.

MR. FEINLEIB: Well--

CHAIRMAN BRANDT: Don't try to disguise something.

MR. FEINLEIB: The estimates you're using for the frequency of use and the amounts of use, I'm trying to get a handle on how that might mesh with marketing projections, but I don't know who to ask for that kind of information.

CHAIRMAN BRANDT: We'll try to get that in a little bit. Okay. You keep coming back. You're trying to hit that stuff. Okay. Any other questions about the FDA's presentations? Yes, Dr. Blaner.

DR. BLANER: Can I ask a question of Dr. Vanderveen? And it may be a semantic question. Your first slide refers to decreased tissue stores of carotenoids. Is that what this is really about or is it blood levels or tissue levels or active levels? You used that term "tissue stores." I'm not sure that we've--do we have any data on that?

DR. VANDERVEEN: No. I'm not sure that we know from my reading, and my view is that we really don't know necessarily what blood levels mean relative to tissue

stores, but I review blood as a tissue, and so I can put it, obviously the transportation of carotenoids is by the blood system, and I would assume that, well, there's evidence in the literature. I don't know that complete deprivation of carotenoids in the diet will lower the blood levels, but they will sustain for some period of time so you would assume there is some depletion of other tissues in the body, and that was--I was merely repeating the facts that seemed to be evident from animal studies and other information we had at the time of rulemaking.

DR. BLANER: I guess I was questioning even semantically the word "store." Indeed blood levels do seem to, when you go off carotenoids, do seem to drop and tissue levels presumably follow. But I guess I'm questioning the use of the word "store." Do we really think carotenoids are stored?

DR. VANDERVEEN: If you consume large amounts of carotenoids, you will turn orange, and obviously the carotenoids are being stored in the cells that are close to the skin at that time and elsewhere in the body, I'm sure.

DR. BLANER: Well, they're being deposited there certainly, but I guess it's a semantic question.

DR. VANDERVEEN: Well, all right. It's a semantic issue. Okay. I take, I understand your point.

CHAIRMAN BRANDT: So if you turn orange, you've

got a lot of it.

DR. VANDERVEEN: That's right.

CHAIRMAN BRANDT: That's good to know. Okay. Any other questions? All right. Hearing none, now we will turn to Dr. Fukagawa and Dr. Feinleib's persistent question about market. Okay. Who's going to respond from P&G?

DR. PETERS: I don't have a marketing hat so just bear with me.

CHAIRMAN BRANDT: Neither do they so you're close enough.

DR. PETERS: Oh, okay. So I'm in good company. My understanding is that if you look at the snack food associations publications that have tracked introductions of different brands over the past years, and you take a look at some of the major winners, if you will, some of the blockbuster introductions in this type of snack food, for example, the baked Lays product, they've achieved a market share of somewhere in the range, and don't shoot me out there if you're out there, Frito-Lay, of eight percent or so of the snack food market.

So if you look at olestra as being a similar kind of a product, if it's used--we got wonderful trial and so forth and so on--if it tracks along at that rate, we would expect to achieve the same kind of a stable share at some point in time. So you know we're already pretty much, based

on the telephone follow-up calls from Indianapolis, at a fairly stable rate at least in that community over the past year. You typically see these nice surges in interest as something is introduced, and then it plateaus off and people adopt, you know, the more consistent users adopt a pattern fairly quickly after they learn about the product, but that's kind of where we are at this point. So it's not a Sherwin Williams ad with cover the globe. It's more of a, you know, it's a healthy percent of one segment of the market. About eight percent is about the best we can go for right now.

CHAIRMAN BRANDT: Dr. Benedict.

DR. BENEDICT: With respect to that, before you sit down, when we talk about a market share of eight percent, I think, I mean I know less about marketing than anyone in the room, does that not mean that eight percent of the population is a consumer, but if you take any one of those members of that eight percent, you might have a 100 percent market share in that household, and so if we're talking about individuals who could potentially be affected by the product, of that eight percent it's possible that 100 percent of them are eating baked Lays or only some other things; is that a fair representation?

DR. PETERS: That's a fair representation and that's, you know, where we are with the surveillance program

is we are looking at people, real life people eating what they're eating, and, you know, the data, the numbers are what they are. But you've correctly represented it.

CHAIRMAN BRANDT: Dr. Underwood.

DR. UNDERWOOD: He just asked my question.

CHAIRMAN BRANDT: Okay. Dr. Clydesdale.

DR. CLYDESDALE: On the study at Hutchinson, I was curious. On the protocol, will there be an opportunity, the people you get, will they be exposed to the national rollout of all these products? So that you might get a higher level of use?

DR. THORNQUIST: Yes, I mean they are exposed to the national rollout of these products which has already begun, of course.

DR. CLYDESDALE: Okay. But you said that you've already done the telephone survey with them or?

DR. THORNQUIST: What we have completed are the baseline visits on these people, but recall that we do repeated cross-sections. So a year from this fall we begin the first cross-section of people who will have had exposure to olestra, then we'll have a second cross-section year after that, and a third cross section after that.

DR. CLYDESDALE: Okay. That's what I was confused about. So a year from now actually the first cross section will be done?

DR. THORNQUIST: Actually for the subsequent cross-sections, we're bringing them in over the course of a year so, in fact, the first year's, the first full year's worth of cross-section will be done in September or O\october of '99, I guess.

DR. CLYDESDALE: Okay. Thank you.

CHAIRMAN BRANDT: Dr. Clancy.

DR. CLANCY: Yeah. I would like to ask some more specific questions because I'm not following what you told Dr. Benedict. It's the marketing question. I'm sorry. It's a marketing question. As I understand it, eight percent--could you help me understand that--are you using market--the market that you're looking at is the entire market for all savory snacks, all pretzels, potato chips, corn chips, crackers?

DR. PETERS: No, it's within a snack food category.

DR. CLANCY: That's my question.

DR. PETERS: Yeah.

DR. CLANCY: What category is that?

DR. PETERS: That's for the potato chip category.

DR. CLANCY: Okay. Now what about the other sector categories within savory snacks?

DR. PETERS: I'm sorry. I've been clarified by my XO brain here.

DR. CLANCY: Okay.

DR. PETERS: It includes corn and tortilla products and pretzels.

DR. CLANCY: Right. But it doesn't include, but it does not include crackers? Is that true? At least my reading of Snack Food Magazine for many years would tell me it doesn't include crackers.

DR. PETERS: That's correct.

DR. CLANCY: That's a separate market. Now what is the market share that you're proposing, that you're hoping to get to in crackers, for example?

DR. PETERS: Well, I'm not proposing that we're hoping to get to anything. I'm just trying to reflect what's currently known about the market share for products like this. And I cited the example of baked Lays at an eight percent share, and I don't have the number for you for national percent share for an olestra containing product, nor do I have the specific information for crackers. I can see what we can find out to give you some perspective or examples.

DR. CLANCY: So my other question is how does the eight percent market share assuming that's what you had translate between 15 percent of the people say in Indianapolis or Marion County eating an olestra product? I can't figure out what the congruence is between those two

numbers.

DR. PETERS: Well, an eight percent share just means that eight percent of the products that go off the shelves are that particular product.

DR. CLANCY: Right.

DR. PETERS: And it does not equate with what fraction of the population--

DR. CLANCY: Right.

DR. PETERS: --of the 15-1/2 percent of the population that might be trying it.

DR. CLANCY: Okay.

DR. PETERS: And as Dr. Benedict pointed out, in any given household, they might have switched entirely to that product.

DR. CLANCY: Sure.

DR. PETERS: And so that's what we're looking for when we try to find these people to enroll in the study is where are the eaters, who can we put in the cohort that's the heaviest consumption group?

DR. CLANCY: So I understand is it because it's proprietary information that you can't tell us what your market share is in any of the sites in which you are present right now?

CHAIRMAN BRANDT: Remember they only market Pringles. They're not marketing Frito-Lay products and

others.

DR. CLANCY: Right.

DR. PETERS: We'll give you the data for Pringles because that's something we own.

DR. CLANCY: Okay.

MR. SEAR: My name is Billy Sear. I'm the marketing person.

DR. CLANCY: Oh, good.

[Laughter.]

MR. SEAR: We look at market shares for each of the subsegments so in the potato chip market, the share that we're seeing from all of the snacks that are in the market today is about a six percent share roughly. It goes up and down depending on what period you're looking at and what all the competitive activity is that's going on in the market. The share in the tortilla market is a little bit lower than that because right now there is only one brand, one product in the market. There is only the doritos versus in the potato chip market, there is the Lays, the Ruffles, and the Pringles. So there is a wider range of alternatives for the consumer.

But given that the price premiums are roughly the same for the products, the taste acceptance for the products is about the same. One can assume that the market share you would capture in one segment would be comparable to the

market share you would capture in all the different segments that you would get within the salted snack category. So potato chips, tortilla chips, corn chips or crackers, the shares would be roughly the same. And so in the aggregate you would end up with a market share of, you know, call it six percent across all the salted snacks categories based on the data that we have from Indianapolis. The national data is obviously yet to be seen.

CHAIRMAN BRANDT: Dr. Jacobson, do you have a comment?

DR. JACOBSON: Well, I certainly don't want to question Mr. Sear, but the A.C. Neilson data from Indianapolis beginning in, the introduction I think was March of 1997, showed about a 7-1/2 percent market share early for all olean potato chips. It declined steadily through the year to about three percent, and I understand it may be up a little bit because of the national marketing and more publicity. That's potato chips, and tortilla chips, as I recall, it peaked at around six percent of the market. The Olean Wow tortilla chips peaked at around six percent of the pounds, not dollars, but pounds of tortilla chips, and that declined steadily through December to, I think, slightly under one percent of the market.

DR. CLANCY: Thank you both.

CHAIRMAN BRANDT: Okay. Thank you all. Now, Dr.

Blackburn had a question for Dr. Mark Brown earlier today and now Dr. Brown is here. So Dr. Blackburn, have at him.

DR. BLACKBURN: I just commented this morning that we were presented with two analyses done independently of Procter & Gamble yesterday that seemed to confirm each other and when I raised the issue this morning, Procter & Gamble suggested that Dr. Brown's analysis was hopelessly confounded and then we had a little tete-a-tete between FDA and Procter & Gamble whether we should use linear, monotonic model or quadratic or the smooth data. And I just thought Dr. Brown ought to have an occasion to respond.

DR. BROWN: Well, I'm glad it's not a carotenoid question because--unfortunately, I was off this morning getting the information that came up yesterday that was in reference to a quote about rates of, the number of people that have been withdrawn from a trial or whatever, and I--

CHAIRMAN BRANDT: That's been straightened out.

DR. BROWN: Okay. I understand that. I didn't understand that this morning so I went on apparently a somewhat less than totally useful mission, but I put together a package that included that analysis of the severity of olestra's effects to the average consumer based on what the eight week clinical trials that I talked about yesterday. And in that package, which you all received, it shows that--the slides that I used today--that shows the

data laid out day by day by each subject for the three key symptoms, and, you know, you can see each day whether they had one of the three key symptoms of diarrhea, loose stools or fecal urgency. You can look at that. And it gives the reference where that data was pulled from. You know what can I say? I just plotted the data that appeared in one of FDA's, in P&G's reports.

And I think that the thing that struck me yesterday was I did this analysis on my own and came to my own conclusions about to be able to predict what kinds of rates you would expect in further studies such as the six week home consumption study that we heard about yesterday, and I kind of made certain predictions which I think were amazingly borne out by FDA's own analysis by its staff scientists that we heard of yesterday in terms of what actually happened in the six week study, in the six week home consumption study.

And I think the point is that looking at the data from these eight week clinical trials allows you to predict fairly accurately, I think, the kinds of rates, both qualitatively and quantitatively that we're seeing in the home consumption study. And I think FDA's analysis bore that out. Thank you.

CHAIRMAN BRANDT: Okay. All right. We're going to--I'm sorry. You got your hand up or are you just

waiting? Okay. We're now going to turn to--we have three people that will not be here tomorrow, Drs. Crouch, Bernstein, and Hubbard. Short-term memory is going, too. We would like to hear your comments on the basis of what you have heard and so forth, what your thoughts are and specifically relevant to the questions that were posed. Does everybody have a copy of those? You should have a copy of them that were part of a charge given to us, and so Dr. Hubbard, you've been here for two days, can you address some of these questions? Do you have them there, sir?

The first one has to do with based on new data or other information, are there any significant unanticipated GI effects captured in the passive surveillance reporting or in the post-marketing studies that could be attributed to the ingestion of olestra and that are adverse to health?

DR. HUBBARD: Okay. My assessment in response to material presented here is that there were no data or other information presented that were indicative of unanticipated events. It is well known that there is an increase in frequency of bowel movements and potentially the so-called looseness of the stools. Both of those could be adequately predicted and there may be a dose response in relationship to the amount of olestra containing product consumed.

In my opinion, these would not entail a significant health risk or adverse event, and it can be

controlled by the subject easily and at their own desire as to what level of, I guess, GI symptomatology that they would like to undertake.

CHAIRMAN BRANDT: All right. What about question number two? Do the new data and so forth show the consumption of savory snacks containing olestra has a significant adverse effect on health and so on?

DR. HUBBARD: The current data--again, I heard of no data that went to further identify a significant event associated with decreased vitamin levels, especially when consumed with the fortified or supplemented olestra containing products. I think that there needs to be some recognition of the confounder associated with the co-consumption issues that have been discussed, and that as we try to design and interpret future studies, attention has to be given to the issue of co-consumption both in terms of the olestra containing products, other fat-free containing products, and the total amount of fat in the meals that are under co-consumption in order to adequately interpret the data.

CHAIRMAN BRANDT: Okay. You haven't heard anything on the labeling yet. That's not till tomorrow so we won't go into that. Dr. Crouch, I'm not sure when you got here so I can't--

DR. CROUCH: Right. I came in for the afternoon

session so I did not hear the morning session.

CHAIRMAN BRANDT: Okay. Then the only one that you can really comment on is question number two. You have that there?

DR. CROUCH: Yes, I do, and from listening to what's been presented, I don't feel that there is new data that is conclusive on the subject of the carotenoids. It's obvious that particularly with the macular degeneration area that there is a great deal of work yet to be done, and I think one of the things that does concern me is that probably attention needs to be paid to the older population and the effect of this product on the older population since that's where you see this disease, but there was nothing in what was presented that was conclusive to my mind. I really defer though to Dr. Bernstein who is a real expert in this area.

CHAIRMAN BRANDT: Well, that's good because that's who I'm getting ready to call on.

[Laughter.]

CHAIRMAN BRANDT: All right. Dr. Bernstein, you were here all day; were you not?

DR. BERNSTEIN: I came here midway through the morning session.

CHAIRMAN BRANDT: Okay. Do you feel comfortable with commenting on question number one with respect to GI

effects? I mean--

DR. BERNSTEIN: No.

CHAIRMAN BRANDT: GI system is hooked to the eyes, I assume.

DR. BERNSTEIN: I don't think you need my opinion on that.

CHAIRMAN BRANDT: Okay. You want to give--

DR. BERNSTEIN: It's all in the eyes of the beholder.

CHAIRMAN BRANDT: --comment of section two?

DR. BERNSTEIN: I'd like to comment. In terms of carotenoids and the eye and the macula in particular, there certainly is a biological plausibility that carotenoids, particularly lutein and zeaxanthin, are important for macular health. They are specifically concentrated in the macula. They are good antioxidants. They may be light-screening compounds. There may be other mechanisms that we don't understand, but clearly there is some reason that they are being concentrated in the macula.

There is some pretty good epidemiological data that carotenoids may be protective against macular degeneration. In particular, the eye disease case control study that was done by Dr. Seddon and others is a very good one. There have been others, and I would like to point out in terms of that study that that study looked only at the

wet form of macular degeneration. And other studies such as the one by Mares-Perlman included only about 16 percent of the wet form. And so that can in comparing different studies with different methodologies and different populations, that's why you may get very different results in these studies.

It's also very clear from other studies that have been done that macular pigment can be affected by diet. Those studies have come out relatively recently just in the past few years, but at least supplementation with possibly what would be considered pharmacological doses of lutein and zeaxanthin can affect the levels of macular pigment. There are no prospective studies done yet. Prospective studies on macular degeneration, any interventions are very, by nature of the disease require large populations, lots of money and long times to do.

At least as ophthalmologists, the current practice right now or the preferred practice is to recommend to patients at risk for age related macular degeneration that they consume more fruits and vegetables. That's one of the few interventions we have that we can offer to patients, and that certainly is specifically tied in. We want them to consume vegetables enriched in lutein and zeaxanthin.

In terms of the effects of olestra on macular pigment, that data needs to be looked at, and I certainly

applaud that Procter & Gamble is beginning to look at that data, and I think obviously there needs to be more done on that.

CHAIRMAN BRANDT: Would you like to specifically give your view about whether or not these data show that consumption of savory snacks containing olestra has a significant adverse effect on health due to the interference of absorption of fat-soluble vitamins or other lipophilic substances?

DR. BERNSTEIN: Right. Certainly my concern would be, as I said, we as ophthalmologists are encouraging people to increase their intakes of lutein and zeaxanthin. If by taking olestra, if the data shows that it's counteracting that, then I certainly would not favor my patients taking that. I'm not sure the data is there. The data I've seen today hasn't specifically shown that it really depletes it, and we probably need to see prospective data looking at macular pigment levels in patients who are taking olestra for a long time. It takes a long time, on the order of the studies that have been done, it takes weeks to months to see a change in macular pigment even with pharmacological doses of these. So by nature, we'll have to be looking at patients who have been eating these savory snacks for possibly a year or two.

CHAIRMAN BRANDT: I don't want to put words in

your mouth, but as I understand it, you have seen no data that it has a significant adverse effect on health?

DR. BERNSTEIN: Not yet, no.

CHAIRMAN BRANDT: All right, sir. That's all you can talk about is what we got now.

DR. BERNSTEIN: Okay.

CHAIRMAN BRANDT: Okay. That done, we're now open for committee discussion and questions and all the other stuff that you all want to do. You're staring at me, whatever that means.

DR. CHASSY: I just wanted to follow up.

CHAIRMAN BRANDT: All right, sir.

DR. CHASSY: I just wanted to note or maybe ask Procter & Gamble because I don't have the partition coefficients, is it correct that the zeaxanthin and the lutein that we refer to in macular degeneration are two carotenoids that we don't expect to be very much absorbed by olestra consumption?

DR. PETERS: I'm sorry. I didn't see who asked the question, but I heard what it was. The answer is they would be less affected than the other carotenoids, beta carotene, alpha carotene. As I mentioned, they are a thousand-fold less lipophilic, and the data we have from the control trials where they're consumed concurrently with olestra, under those controlled conditions, we saw a third

to a half the level of the effect that we saw for the hydrocarbon carotenoids, alpha and beta carotene, lycopene.

CHAIRMAN BRANDT: We still got coming attractions. Dr. Feinleib.

MR. FEINLEIB: This is actually a question, I think, for Dr. Rulis or somebody from the FDA. Everything we've been discussing concerns the use of olestra in savory snacks and the distribution, et cetera, of the consumption of savory snacks. I think part of our discussion a little bit earlier about market shares, et cetera, was really to try and get a handle on the potential consumption of olestra in any form by the general population.

CHAIRMAN BRANDT: I'm sorry. But that's really out of the question because they are not approved to do anything else nor have they asked for approval, and so we don't need to address that issue.

MR. FEINLEIB: Well, my question is what steps would be necessary if they were to expand the use of olestra?

CHAIRMAN BRANDT: They have to go through the approval process just like they went through it for this savory snack stuff.

MR. FEINLEIB: Thank you.

CHAIRMAN BRANDT: Okay. So there is--I don't think we need to speculate about whether or not we're going

to eat it in brownies and other kinds of stuff in spite of the fact that people fight over them. So that, you don't need to answer it, Dr. Treibwasser. We don't want to know what you're going to do.

[Laughter.]

DR. TREIBWASSER: Thank you.

CHAIRMAN BRANDT: Okay. Are there other? Yes, Dr. Jacobson.

DR. JACOBSON: Well, this is a larger question. I think maybe for Mr. Levitt. The way that Dr. Brandt asked Dr. Bernstein about his position on this issue seemed to put the burden of proof entirely on Dr. Bernstein to agree that there was adequate proof that the loss of carotenoids is harmful. I think the way the law is that the petitioner has to sustain the view that there's a reasonable certainty of no harm. And I think all the questions need to be carefully phrased, and I think better phrased.

DR. LEVITT: We actually took some care in framing the questions. And I'm satisfied with the way the questions are framed for this reason. As I said in my opening, what we're doing here today is not going back and doing an initial review decision of the product. What we're really asking is in the last two and a half years, what's changed? And so each of the questions, as you'll see, is phrased based on the new data since January 1996, da-da-da-da-da,

based on the issue we're talking about.

And so here the real question is are there data that have existed since January 1996 that changes the landscape? That changes what we know about risk or the safety of this product? That's what we need to focus on here.

DR. JACOBSON: I'm not questioning the date at which you're choosing. I may quibble a little but the question still remains, you know, within the last two and a half years, does Dr. Bernstein have to agree that there is proof of harm? I don't think so. I think he has to state an opinion as to whether based on the new evidence, there is still reasonable certainty of no harm?

DR. LEVITT: What you're getting at is, and I have to say we're connecting but not agreeing--

[Laughter.]

DR. JACOBSON: Tell me the connection.

DR. LEVITT: The connection is that what you're saying suggests that you want to go back and have what I would call a de novo decision on the entire scope of issues here. And while I certainly don't want to put all the burden on Dr. Bernstein, what we are trying to ask Dr. Bernstein and all the others again is the FDA has already made a decision that the body of information as of a couple of years ago showed a reasonable certainty of no harm. So

we go into this meeting today or this week with that as a given. Now, for people who didn't agree with that conclusion, you're obviously free not to agree with it.

But is a conclusion the agency reached, and therefore this discussion for it to be useful to us and what we have to do is to focus on what if anything has changed? We at the time of the approval, and as folks know I'm relatively new in this job, so was totally, you know, uninvolved at the time, but what the agency said was we want to be sure that with a compound of this type that there is further surveillance studies, et cetera, done on the product, and that certainly has been done, you know, to the extent that we've seen, and we've had two days of presentations on information that has developed from then and now.

So the question we really want to know now is, as I said, based on the new data, does this change the initial decision? But in order to have that discussion, you need to accept what the initial decision was. If you don't accept the original finding of reasonable certainty of no harm, then you're not going to like this discussion. And I'm--

DR. JACOBSON: Well, who would disagree with the original decision? But the Federal Register says the agency would only need to show that based upon new evidence, FDA is no longer able to conclude that the approved use of olestra

is safe. That is that there is no longer a reasonable certainty of no harm from the use of the additive.

DR. LEVITT: Right.

DR. JACOBSON: And it would seem like that's the question to ask to get advice from the members of the committee.

DR. LEVITT: Right. And I would postulate that if as of the state of knowledge two and a half years ago that the agency reached the conclusion there is a reasonable certainty of no harm, and if the new data since then don't present new safety concerns, then I'm hard-pressed to figure out how we don't still have and maintain a reasonable certainty of no harm? But I think the thought process needs to be, you know, this is the level we were at on January 1996 that showed a reasonable certainty of no harm. Is there something new above that since that that's changed, that's going to change that? But I think we've got to start with that.

That has nothing to do with your concern over where the burden of proof is in the statute. I think it has to do with where we are in doing a post-marketing check. As I said in beginning, I think everybody recognizes and accepts that the statute requires there be a finding of reasonable certainty of no harm, that it's the petitioner's job to do that, and it's the agency's conclusion two and a

half years ago that that was achieved. And so when we are looking at products after they've been in marketing, we have to really focus on what's new, what's changed; does that alter the original discussion? Does that alter the initial conclusion, I mean? And that's what we're trying to do, and I have to say that at least my observation from sitting through nearly all of the first two days is I really have to commend everybody; people have really tried to do that, tried to present what is the new information, tried to critique it, try to debate on what it means. And we'll look forward to further discussion today and tomorrow in terms of where that takes us.

CHAIRMAN BRANDT: Okay. Are there other questions or comments from the committee? Dr. Byers.

DR. BYERS: When we accepted this charge, I accepted it in the spirit in which you just now described it, that a decision was made that there was reasonable certainty of no harm and we were here in order to revisit that in the context of new information. However, if you read the second question, it's quite different, as Mr. Jacobson points out. It says do the new data from the first year of active surveillance or any other newly available data show that consumption of savory snacks containing olestra has a significant adverse effect on health due to interference with absorption of fat-soluble vitamins or

other lipophilic substance?

In other words, the question is very much more specific than that and really requires a different kind of conclusion. I don't want to quibble about this charge because we all accepted it and we understand it. But I think the point that Mr. Jacobson made is a valid one, and that is this question is not just to revisit the question of reasonable certainty of no harm considering the new data, but you've actually charged us with a very specific question that says is there scientific proof now of harm?

CHAIRMAN BRANDT: No, no. No, no, he doesn't say that.

DR. LEVITT: I don't think that's what it says.

DR. BYERS: Well, it says do the new data show that consumption of olestra has a significant--do the new data show that consumption of this has a significant adverse effect on health?

DR. LEVITT: I'm sorry. Could you just repeat that? I--

DR. BYERS: Well, you know the question. You wrote it. I was simply pointing out that I frankly didn't realize this subtle but probably important distinction between the issue of reasonable certainty of no harm and the charge given to us in this question, and it is very much more specific with regard to is there new data in the last

two years or year and a half or two years that show that consumption of this material has a significant adverse effect on health? That's what we're being asked--and we will give answers to that.

DR. LEVITT: Right.

DR. BYERS: But I think the point is correct, that this is quite different from reasonable certainty--

DR. LEVITT: Well, I understand the point. That's why I said I think we understand each other, but, you know, this is a scientific committee and we're trying to pose a scientific question.

DR. BYERS: Well, the reason I spoke up--

DR. LEVITT: This is the committee that will help us reach the regulatory conclusion.

DR. BYERS: The reason I spoke up is this. Because when you went on to describe, you were describing a process that would be a process we would use in coming up with a conclusion about reasonable certainty or not. But in fact, this question is much different than that, I think.

CHAIRMAN BRANDT: Okay. Dr. Lamm.

DR. BYERS: That's my opinion.

DR. LAMM: Dr. Jacobson, will Dr. Colditz's comments be available to us in some written form for us to contemplate this evening as we consider the answers to these questions?

DR. JACOBSON: We'll let Dr. Colditz answer that.

DR. COLDITZ: I've already handed over a copy of my slides to the transcription staff, but they could be copied if you wanted.

CHAIRMAN BRANDT: There is no requirement that he provide a written transcript, and he will make copies of slides. Dr. Chassy, does that mean you're safe? Okay. Other questions? Comments? Hearing none, we are going to begin in the morning at 7:45. That's 15 minutes earlier. We will discuss primarily labeling tomorrow, following which--hang on, hang on--following which each of you will be asked to address these three questions. I would hope as briefly as possible but feel free to elaborate and all that kind of stuff, if you want to.

And the final thing is be sure you eat fruits and vegetables tonight. Sorry. Excuse me. I forgot administrative stuff.

DR. LARSEN: The question has come up as to whether the committee has been given a copy of the Fred Hutchinson report. They tell me that it was mailed to us and so on. That theory that we received it, it should be in here, but we're still trying to check so you have it for tonight.

CHAIRMAN BRANDT: Okay. All right. We are now recessed till 7:45 in the morning, not tonight.

[Whereupon, at 5:30 p.m., the meeting recessed, to reconvene at 7:45 a.m., Wednesday, June 17, 1998.]

CERTIFICATE

I, **VICTORIA S. McLAUGHLIN,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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