DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE MEETING

Advice on CFSAN'S Draft Report:

Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food

Wednesday, July 13, 2005

8:30 A.M. to 5:50 P.M.

Greenbelt Marriott
6400 Ivy Lane
Grand Ballroom

Greenbelt, Maryland 20770

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

FOOD ADVISORY COMMITTEE STANDING MEMBERS:

Richard A. Durst, Ph.D. - Acting Chairman
Jeffrey A. Barach, Ph.D. (Industry Representative)
Patrick S. Callery, Ph.D.
Dennis Gonsalves, Ph.D., M.S.
Jean M. Halloran (Consumer Representative)
Douglas C. Heimburger, M.D., M.S.
Margaret C. McBride, M.D.
Mark Nelson, Ph.D. (Industry Representative)
Carol I. Waslien Ghazaii, Ph.D., R.D.

TEMPORARY VOTING MEMBERS:

Petr Bocek, M.D., Ph.D.
Margaret Briley, Ph.D., R.D.
Erica Brittain, Ph.D.
Ciaran P. Kelly, M.D.
Soheila June Maleki, Ph.D.
David O. Oryang
Marc D. Silverstein, M.D.
Suzanne Teuber, M.D.

FOOD AND DRUG ADMINISTRATION:
Catherine Copp, J.D. - Senior Policy Advisor
Food and Drug Administration, CFSAN

Steven M. Gendel, Ph.D. - Senior Scientist
Food and Drug Administration
National Center for Food Safety and Technology

Rhonda Kane, M.S., R.D. - Consumer Officer
Food and Drug Administration, CFSAN

Michael M. Landa, J.D. - Deputy Director for Regulatory Affairs
Food and Drug Administration, CFSAN

Stefano Luccioli, M.D. - Senior Medical Advisor
Food and Drug Administration, CFSAN

Marcia Moore, Food Advisory Committee, Executive Secretary

Jenny Slaughter - Director
Food and Drug Administration Integrity and Ethics Staff

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

GUEST SPEAKERS:

Rene Crevel, Ph.D. - Senior Scientist
Unilever, Safety and Environmental Assurance Centre, United Kingdom

Susan Hefle, Ph.D. - Associate Professor and Co-Director
Food Allergy Research and Resource Program, University of Nebraska

Stefano Luccioli, M.D., - Senior Medical Advisor
CFSAN, FDA Assistant Professor, Georgetown University

Anne Munoz-Furlong
Director, Food Allergy & Anaphylaxis Network

Steve Taylor, Ph.D. - Maxcy Distinguished Professor & Director
Food Allergy Research and Resource Program, University of Nebraska

Robert Wood, M.D. - Professor
Johns Hopkins University School of Medicine

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

CALL TO ORDER, WELCOME, AND INTRODUCTIONS

CHARGE TO THE FOOD ADVISORY COMMITTEE

CHAIRMAN DURST: I would like to call the meeting to order.

Good morning. I am Dick Durst, professor of chemistry in the Food Science and Technology Department at Cornell University. I was asked to chair this meeting over the next two and a half days. I would like to make a few announcements before we begin our meeting this morning.

I would appreciate it if everyone would turn off their cell phones, unless they are expecting a call of a super emergency nature. I would also like to ask if the guest speakers could make themselves available for the discussion this afternoon, I would really appreciate it. We may have some additional questions.

We have received a charge from the FDA to give our evaluation of the draft report prepared by the Threshold Working Group. I assume all of the members have read that thoroughly. In my opinion,

I it was fascinating.

It was an excellent article and I commend the Committee for coming up with it. It was very educational. Not being an expert on food allergens myself, it was extremely educational, and I was able to follow it quite clearly.

Our charge is to evaluate this report to determine whether the approaches that are presented in there are the only ones or the better ones, which of the ones that are in there might be the most appropriate. This is the focus of our meeting today, both on the food allergens and on gluten.

Let me also begin by asking the committee members to introduce themselves. We will start with Dr. Silverstein.

Marc, would you start it off?

DR. SILVERSTEIN: Good morning. My name is Marc Silverstein, and I'm a general internist and geriatrician at Baylor Health Care System in Dallas.

DR. TEUBER: Good morning. My name is Suzanne Teuber, I am an allergist at UC-Davis.

MR. ORYANG: Good morning. I am David Oryang. I am a risk analyst and agricultural engineer at the United States Department of Agriculture, Animal and Plant Health Inspection Service.

DR. KELLY: I am Ciaran Kelly, and I am a gastroenterologist at the Harvard Medical School in Boston.

DR. MALEKI: I am Soheila Maleki. I am a scientist with the USDA.

DR. BRITTAIN: Erica Brittain, I am a statistician at the National Institute of Allergy and Infectious Disease.

DR. BRILEY: Margaret Briley, University of Texas at Austin, nutritionist.

DR. BOCEK: Good morning. I am Petr Bocek, medical officer in NIH's National Institute of Allergy and Infectious Diseases.

MRS. MOORE: I am Marcia Moore. I am with the FDA as the executive secretary of the Food Advisory Committee.

DR. WASLIEN: I am Carol Waslien. I am a

nutritional epidemiologist at the University of Hawaii.

DR. McBRIDE: I am Margaret McBride. I am a child neurologist at Akron Children's Hospital.

DR. CALLERY: I am Patrick Callery, a pharmaceutical scientist from West Virginia University.

DR. GONSALVES: I am Dennis Gonsalves, a scientist with USDA in Hawaii.

DR. HEIMBURGER: I am Doug Heimburger, a physician and nutrition specialist at the University of Alabama at Birmingham.

DR. BARACH: Jeff Barach with Food Products Association, vice president for special projects and regulatory affairs.

DR. NELSON: Mark Nelson with the Grocery Manufacturers Association responsible for regulatory and scientific policy.

MS. HALLORAN: Jean Halloran from the Consumers Union where I am director of food policy initiatives.

CHAIRMAN DURST: Thank you very much.

One other item is that we may have some of our members leave early on Friday, depending on the amount of time we can spend. What I propose is that today and tomorrow that we anticipate having to go perhaps till 6 o'clock so that we can be sure that we have enough time for all of our discussions.

Okay. Let me introduce our first speaker. This will be Jenny Slaughter, director of Ethics and Integrity Staff at the FDA, to describe the "Conflict of Interest Statement" and other instructions.

CONFLICT OF INTEREST STATEMENT

AND OTHER INSTRUCTIONS

MS. SLAUGHTER: Well, good morning and welcome. The Food and Drug Administration is convening today's meeting of the Food Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members of the Committee are special government employees or regular Federal

employees from other agencies subject to Federal conflict of interest laws and regulations.

FDA has determined that members of this Advisory Committee are in compliance with Federal ethics and conflict of interest laws including, but not limited to, 18 U.S.C. 208 and 21 U.S.C. 355 and 354.

Under 18 U.S.C., Section 208, applicable to all government agencies, and 21 U.S.C. 355, applicable to only FDA, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for particular interventional services outweighs the potential conflict of interest.

Members who are special government employees at today's meeting including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest of their own as well as those of their spouse, minor child, and employer, which are related to the discussions of today's and

tomorrow's and Friday's meeting regarding the "FDA Draft Report: Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Foods."

These interests may include investments, consulting, expert witness testimony, contracts, grants, research and development agreements, public speaking, writing, patents, royalties, and primary employment.

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to the following participants, Dr. Suzanne Teuber and Dr. Soheila Maleki, please note that all of the interests in the firms that could potentially be affected by the Committee's decisions.

A copy of the written waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, the following individuals are participating as FDA's invited guest speakers, July 13th: Dr. Rene Crevel, Dr. Susan Hefle, Anne Munoz-Furlong, Dr. Steve Taylor, and

Dr. Robert Wood.

The following individuals will be participating as FDA invited guest speakers tomorrow, July 14th: Dr. Pekka Collin, Dr. Alessio Fasano, Dr. Donald Kasarda, Dr. Cynthia Kupper, and Dr. Joseph Murray.

Lastly, I would like to report that Dr. Jeffrey Barach and Dr. Mark Nelson are serving as the industry representatives on the Committee at today's meeting. They are acting on behalf of all regulated industry.

Dr. Jeffrey Barach is employed by the National Food Processors Association and Dr. Mark Nelson is employed by the Grocery Manufacturers of America.

A copy of this document will be placed on the back table, if anybody wishes to take a look at it. I thank you.

CHAIRMAN DURST: Thank you very much. We will now go on to the welcome and opening statement by Dr. Michael Landa, the deputy director for Regulatory Affairs at CFSAN, the FDA.

Mike.

WELCOME AND OPENING STATEMENT

MR. LANDA: Thank you, Dr. Durst. You will be pleased to learn that I don't have a doctorate or an M.D. I'm just a plain, old J.D.

(General laughter.)

MR. LANDA: Thanks again. Good morning to everyone. Welcome to the members of the committee, to the guest speakers, to members of the public who have joined us today, and to my fellow FDA employees.

I would like to give a special thanks to the Committee members for your willingness to take time from busy schedules to help us with your expertise for a meeting that will be several days long. We are all here today, tomorrow and a fair chunk of Friday.

Let me just add that Dr. Brackett had hoped to be here this morning, but he wasn't able to make it. I am hopeful that he will be here for some portion of the meeting. He was called downtown for a meeting this morning.

I am going to refer to a couple of points on the food allergens, but the points I'm making apply to celiac disease as well. It is just less cumbersome to start with the food allergens. The agenda has been making, I think, an opening statement, of course I'm really not going to do that.

There are just a few points I want to make as you go into your inquiry today. The first is virtually every FDA speaker makes at this kind of proceeding which is what we do really is based on science.

We talk about being a science-based agency. It is the bedrock; it is the foundation. In that context, I am going to paraphrase what may be a rather obscure 19th century Senator, Karl Shrews from Pennsylvania.

The paraphrase essentially is, Our science correct or incorrect, when it is correct, help us keep it correct; when it is incorrect, help us to correct it. That is as much as anything else what we want from you here in terms of your expertise in

the science.

If with respect to the threshold in the Draft Report, we have gotten it right, we want to know from you that we have gotten it right. We want your help in keeping it right. If we have gotten it wrong, we want your help in getting it right. That includes, as you will hear, if we have not considered an approach that we should have considered, we want to know that from you.

The third point I will make is that Americans suffer from food allergies, particularly children. There is some evidence that the number is increasing. If you add to that family members, you really have tens of millions of folks who are involved. At the moment their principle means of protection really is exquisite attention to the food label. That is their pathway to safety I suppose.

We are hoping that eventually thresholds will provide another path to safety. This is the beginning of the inquiry into thresholds, that is, the approaches that are outlined in the report. It

is the first step in a very important process.

The last point I will make is just that this is as much as anything else for members of the public, the docket is going to remain open until about the middle of August.

If people have comments, based on what they have heard today, for example, they should feel free to submit those comments to the docket. Again, it is until about, I don't remember the precise date, but it is the middle of August.

In that connection, I should say we are especially interested, as I think is always the case, in data. In this case, data of the type outlined in the report.

Thank you.

CHAIRMAN DURST: Thank you, Mike. Since Mr. Landa didn't want me conferring a doctorate degree on him, I will not do it with Catherine Copp, who is the policy advisor at CFSAN, also the FDA, who will discuss the use of food allergens thresholds.

USE OF FOOD ALLERGENS THRESHOLDS

MS. COPP: I was hoping. Oh, well.

(General laughter.)

MS. COPP: Thank you, Dr. Durst.

Good morning. As you know, the focus of this meeting today and tomorrow and the discussion on Friday is the Draft Report of CFSAN's Threshold Working Group: Approaches to Establish Thresholds for Major Food Allergens and For Gluten in Food.

I have been asked to provide a context for the Draft Report in terms of CFSAN's programmatic efforts. This is one thing that if I were a real doctor I could do. Lawyer's don't do this.

(Slide.)

MS. COPP: Last August, Congress enacted the Food Allergen Labeling and Consumer Protection Act, which we refer to in-house by the somewhat awkward acronym "FALCPA."

This new law amends the Federal Food, Drug and Cosmetic Act, the principle statute administered by FDA by requiring that the label of a food product that is or contains an ingredient that bears or contains a major food allergen

declare the presence of the allergen as specified in the law. In shorthand, the declaration is to be in "consumer friendly" terms.

FALCPA defines a "major food allergen" as one of the eight foods or food groups or a food ingredient that contains protein derived from one of these foods. Those are listed on the bottom of this slide. By "food groups," I mean fish, tree nuts and crustacean shellfish, which were identified by Congress in the law.

(Slide.)

MS. COPP: The possible existence of threshold levels for food allergens is an important scientific issue, as Mr. Landa has pointed out, associated with our implementation of FALCPA.

Although the law does not require FDA to establish thresholds for any food allergen, there are three possible ways, which are listed on this slide, that such thresholds could be used to implement the new law, these are: administering the petition process provided for in FALCPA, administering its notification process, and

addressing the issue or the occurrence of cross-contact.

(Slide.)

MS. COPP: FALCPA provides two processes by which an ingredient may be exempt from the FALCPA labeling requirements, a petition process and a notification process. I'm trying to read my own slides (laughter). No, okay.

Under the petition process, an ingredient may be exempt, if the petitioner demonstrates that the ingredient does not cause an allergenic response that poses a risk to human health.

Given this language for the petition exemption standard, we believe it will be very important for us to both understand food allergen thresholds and to have a sound scientific framework for evaluating the existence of such thresholds.

Under the notification process, an ingredient may be exempt, if the notification contains scientific evidence that demonstrates that the ingredient does not contain allergenic protein, or, if FDA has previously determined under the food

additive approval process that the food ingredient does not cause an allergenic response that poses a risk to human health.

(Slide.)

MS. COPP: Given this language for the notification exemption standard, we also believe that it will be very important for us to understand food allergen thresholds and to have a sound scientific framework for evaluating the existence of such thresholds.

(Slide.)

Finally, the FALCPA directs FDA to prepare and submit a report to Congress. This report will focus principally on the issue of cross-contact of foods with food allergens and is to describe the types, current use of, and consumer preferences with respect to so-called "advisory labeling." Processed in a facility that also processes tree nuts is an example of such labeling.

Cross-contact may occur during food production when residues of an allergenic food are

present in the manufacturing environment and are unintentionally incorporated into a food. Because the food is not intended to contain the allergen, it is not declared as an ingredient on the food's label. In some cases, however, the potential presence of the food allergen is declared by a voluntary advisory statement.

We also believe that understanding food allergen thresholds and developing a sound scientific framework for evaluating the existence of such thresholds may also be useful to us in evaluating and addressing food allergen cross-contact and the use of advisory labeling.

Thank you.

CHAIRMAN DURST: Thank you very much.

Does the Committee have any questions or discussion of this presentation?

(No verbal response.)

CHAIRMAN DURST: If not, I think we will proceed.

The next speaker is Dr. Robert Wood, professor at Johns Hopkins University School of

Medicine, who will give us an introduction to food allergens.

INTRODUCTION TO FOOD ALLERGENS

DR. WOOD: Thank you very much. It is a pleasure to be here. What I was asked to do is to provide an overview of food allergens and food allergy leading into the discussion that is going to go on over these next couple of days.

(Slide.)

DR. WOOD: The beginning of this, any talk about food allergy really requires that we have some common definition that we can all agree on. This is something that is not as easy as it might sound and often generates a lot of confusion. The reality is that a lot of what is called food allergy is really not food allergy and may fall under more of a food intolerance category.

When we are talking about food allergy, there are a couple of key ingredients. One of them is that there is an immunologic component to the reaction. The reaction is typically to the protein component of the food as opposed to a food

intolerance that is more often related to the carbohydrate component of the food. Importantly to this meeting, exquisitely small amounts may cause a reaction and that these reactions can be severe and even life threatening.

(Slide.)

DR. WOOD: The pathophysiology of the allergic response is sort of very schematically diagramed here. What we are thinking about is a process that begins with exposure and with most allergy, probably all allergy, you have to have some prior exposure to develop your sensitivity.

(Slide.)

DR. WOOD: There is a genetic predisposition that makes some people particularly more prone to develop allergy in general, whether it be food allergy or respiratory allergy, than others. There are some people who no matter what, how, when and where they are exposed they will never develop an allergy, and others who with very trivial exposure may develop a severe allergy.

If you are in this group who is genetically predisposed, your immune system then goes through a process we will refer to as sensitization. Sensitization is most often involving the production of IgE antibodies. We will talk about this in a little bit more detail about some different food allergy syndromes.

However, it is also important to note that not every food allergy involves IgE and that there may be differences in the types of reactions and the doses of food required to induce a reaction in those patients that have IgE versus non-IgE-mediated food allergy.

Once you have become sensitized, then reexposure to this food will lead to symptoms. These symptoms may be abrupt, they may occur within seconds of eating the food, or they may be very low-grade and chronic. This is another concept that we will come back and talk to a little bit.

With some patients it will be very easy to determine a threshold, and in some patients it will be virtually impossible to determine a threshold

because their symptoms will not appear in a challenge test. They may take days or weeks of chronic exposure and then develop very significant disease based on that chronic exposure.

(Slide.)

DR. WOODS: The prevalence of food allergy is substantial. The numbers that we would be most comfortable with would be 5 to 7 percent of young children; 2 to 3 percent of adolescents and adults; at least 10 or 11 million Americans affected.

We do believe that the prevalence is rising. We don't believe that this is specific to food allergy. There has been a substantial rise in asthma and other allergic diseases as well as food allergy.

Now, the reason that these numbers change between childhood and adolescence and adulthood is because a large proportion of food allergy is outgrown over the first five to seven years of life.

(Slide.)

DR. WOOD: There is a long list of

potential food allergens out there. At least 200 foods have been identified and characterized as truly food allergens, but there is a relatively shorter list that are focused upon because they are responsible for the vast majority of food allergy that occurs.

The list on the left-hand side representing what is most common in young children: milk, egg, peanut, soy, wheat, and tree nuts. Then, the list shifts a little bit as you get into older children, adolescents and adults and is dominated by peanuts, tree nuts, fish, and shellfish.

The reason that this list changes from childhood to adulthood is because four of these most common food allergens in your children -- milk, egg, soy, and wheat -- are typically outgrown.

Eighty to 90 percent of children will outgrow those food allergens and not carry them into adolescence or adulthood, whereas the peanuts, tree nuts, fish and shellfish are significantly

more difficult to outgrow, less commonly outgrown, and tend to persist into adulthood and actually through the patient's entire lifespan.

(Slide.)

DR. WOOD: Now, the signs and symptoms of food allergy are highly varied. They may be chronic and low grade as I mentioned, they may be acute and life threatening. What I want to run through in the next couple of minutes are just some examples of allergic reactions that will point out a number of things about not only the kinds of reactions, but the exquisitely small amounts of food that induce these reactions we are going to show you, and the sort of day-to-day issues that patients with food allergy are facing.

(Slide.)

DR. WOOD: The first couple of patients I am going to show you have urticaria or hives. This is a total body hive reaction that this boy is experiencing, a patient I have known since he was an infant.

He is school age at this point. This

reaction occurred when he was in the grade school cafeteria, was being teased about this food allergy, another child blew a straw full of milk across the table into his face, and he had this really significant reaction.

(Slide.)

DR. WOOD: This baby here was identified with milk allergy in the first few weeks of life. There are some children who don't show up with food allergy until they are two or three or four years old, while there are others who are really demonstrating food allergy in the first days of life.

This was a baby who was so allergic that he would react very acutely if his mother, who was breast feeding him, ingested any milk protein. She was on a very strict avoidance diet after we identified his milk allergy, but on the occasion of her birthday ate a piece of cheesecake, breastfed him an hour and a half later, and he had this acute hive reaction.

(Slide.)

DR. WOOD: Now, when we are thinking about urticaria or hives, there are patients that may have chronic urticaria. Food allergy is rarely a cause of chronic urticaria.

However, when someone shows up with an acute episode of hives, the chance that it is food allergy becomes higher. Again, we are looking a relatively short list of foods that are most commonly implicated: peanut, nuts, eggs, milk, fish, and shellfish.

Importantly, these reactions are usually very quick in their onset. Ninety percent of them or thereabouts will have an onset within 30 minutes; at least half of them, within 5 minutes; and virtually all of them, within 2 hours.

When a patient has this type of reaction, it is often very easy to identify the culprit food because of the abrupt association of the ingestion of that food with the onset of these hives.

Then, in more severe episodes, there may be swelling or angioedema or associated gastrointestinal or respiratory symptoms. That is

moving into more of a systemic reaction that we would refer to as "anaphylaxis."

(Slide.)

DR. WOOD: Now, this is a patient here who is having an anaphylactic reaction. When you look at her back here, it looks just like hives. When you see her front, though, she is having swelling and breathing difficulty.

(Slide.)

DR. WOOD: This is a patient who was having a reaction in the midst of a food challenge -- not in the midst of it, after her first tiny dose of egg protein, she went into this very severe, anaphylactic reaction.

(Slide.)

DR. WOOD: This boy here is someone who is having a dramatic episode of swelling. His reaction occurred. Most patients, we should say, who are having severe reactions know about their food allergy and are making efforts to avoid it.

He was shellfish allergic -- he is

shellfish allergic. He was making efforts to avoid shellfish, and he had been reaction-free for several years.

Then, on another birthday occasion, he ate chicken in a restaurant and the chicken had been fried in the same oil as shrimp had been fried. With that cross-contact, this severe reaction.

(Slide.)

DR. WOOD: Anaphylactic reactions are defined as a systemic allergic reaction, involvement of multiple organ systems. These have an abrupt onset typically. They are related to IgE antibodies.

You can identify these by doing a skin test or a blood test looking for IgE. The manifestations are not always severe. There is an impression that all anaphylaxis is life-threatening. Some episodes are relatively mild, but others progress rapidly to life-threatening or fatal reactions.

We think that there are at least 150 deaths in the United States each year due to fatal

food-induced anaphylaxis. That number is probably a substantial underestimation, but we would be very comfortable saying that it is well identified of 100 to 150 deaths per year.

There are different types of reactions: some are single phase and some have two phases, where a patient may look better and then two or three or four hours later have an even more severe reaction than they had initially, some of those lead to the worst outcomes.

(Slide.)

DR. WOOD: This is a patient with one of the more chronic forms of food allergies, the patient with severe itching due to his eczema. In Eczema, a food allergy is often underappreciated because there is not an obvious cause and effect.

This is one where it is more of a low-grade, chronic reaction. Hence, this is much harder for a patient or a family member to identify that, yes, he ate this food and he is more itchy now, rather it is really more of a low-grade reaction where you don't see these direct

relationships between ingestion of the food and the outcome being their eczema or atopic dermatitis.

It is also a condition where food allergy is underappreciated by physicians and where patients may be treated with a variety of different creams and lotions and only later on find out that it was really a food allergy that was driving the eczema.

Overall, 40 to 50 percent of patients with severe atopic dermatitis and 20 or 25 percent with less severe cases have an underlying food allergy.

The same list of foods: egg allergy being most common, followed by milk, peanuts, soy, wheat, and fish. These six foods account for the vast majority of food sensitivities seen in atopic dermatitis.

From our standpoint, it makes it relatively easy to screen patients and find which of them are allergic by testing for a relatively short list of foods.

(Slide.)

DR. WOOD: Now, the last category that I

want to mention is something that we will lump together as gastrointestinal food hypersensitivity. There are a variety of conditions that fall under this umbrella.

There are some that are in the immediate hypersensitivity category. This would be part, say, of an anaphylactic reaction where someone ate food, broke out in hives, had vomiting, diarrhea, abdominal pain, or other gastrointestinal symptoms.

There is another condition called "oral allergy syndrome" where patients have reactions that are confined to their mouth or throat or lips, particularly related to fresh fruits and vegetables.

There is another group of conditions that are lumped under a category of eosinophilic disorders of the GI tract. There is a specific condition, eosinophilic esophagitis, where only the esophagus is involved. As most people in the audience know, the eosinophil is a type of white blood cell that is most affiliated with allergic reactions.

If you take someone who is having a bad hay fever day outside today and look at their nasal secretions, their nasal secretions will be loaded with eosinophils. If you take someone that is having difficult asthma, their bronchial mucosa will be loaded with eosinophils.

By the same token, if you have allergic eosinophilic esophagitis, the lining of your esophagus is loaded with eosinophils. It may be isolated to the stomach, it may be more diffuse where we would call it "allergic eosinophilic gastroenteritis." This is somebody who may have disease anywhere in their GI tract, and oftentimes very diffusely.

There are some other conditions, enterocolitis syndrome and dietary protein proctitis, that are much more common in very young babies.

The importance of presenting these different syndromes here is that some of these syndromes are IgE mediated and some of them are not IgE mediated, some of them are very acute and some

of them are very chronic.

It turns out that those syndromes that are more chronic and low-grade that don't present with any acute symptoms, don't present with any clear cause and effect of eating the food and having increased gastrointestinal symptoms are going to be, potentially, the most difficult for this Committee to grasp. That is because these patients are often reacting to remarkably small exposures.

I will come back at the end to sort of give a couple of examples of the dilemma that kind of patient is going to present to us as we really try to figure out what is safe and what is not safe.

It also turns out in the same vein that the non-IgE conditions in general are probably going to be most difficult to deal with, both because they often don't have the acute IgE-type symptoms, and because they are predominantly mediated by a different part of your immune system that can recognize even smaller degrees of these food proteins that identifying thresholds are going

to be much more difficult.

(Slide.)

DR. WOOD: Now, when we are trying to approach a patient with a food allergy, one of the real difficulties is making an accurate diagnosis. The diagnosis, as in most everything we do, begins with a history, talking about the foods they suspect are causing problems, whether we think the symptoms are consistent with food allergy, whether this is something that may not be food allergy at all, or whether it may be a food intolerance rather than an allergy. We are going to be interested in the timing of the symptoms and the reproducibility of reactions.

It turns out that when you do a very careful history, most of the time it is wrong. It will be correct in the acute reactions, where you have a patient who comes in and says, "I fed him scrambled eggs for the first time last week, and he had hives all over."

"She took her first bite of peanut butter, and developed hives within 2 minutes."

It is very likely that the history will be born out when you do further testing. However, when you look at the bulk of patients with food allergies, many of them will have these more chronic conditions like eczema or the gastrointestinal disorders. When you are looking at those patients, you will only verify the history when you do further testing about a third of the time.

(Slide.)

DR. WOOD: The next set of tests we do after taking a history would typically either be skin testing or serologic testing. A RAST test, "radioallergosorbent test," is the most common serologic test that is used.

These tests have some value and they also have some problems. The problems they have is that there is a relatively high rate of false-positive tests. They do not have a terribly good positive predictive accuracy.

They are generally accurate when they are negative. Although, they will only be active when

they are negative when you are convinced this patient has an IgE-mediated condition, because both of these tests rely on the presence of IgE antibodies to identify the specific food allergy.

An example would be if a patient develops hives or anaphylaxis, which typically are IgE-mediated, and they suspect that it is a certain food. If you get a positive test back, it is very likely that they have that allergy. If you get a negative test back, then you need to keep looking. It was not likely that food that caused that reaction.

However, if you have a patient with something like the allergic eosinophilic gastroenteritis where there may not always be IgE antibodies, you cannot stop with a negative test and say, "We've proven you don't have food allergy." That is something that happens all the time, but it is often going to lead to a misdiagnosis and mismanagement of that patient.

The bottom line is that we need to carefully interpret our tests in the context of the

overall clinical picture, and that we need to rely on oral challenge tests as the more accurate tests, so that we will say that they are not completely definitive. They are more definitive but not completely definitive.

Again, they are going to be less definitive in the patients that have more delayed type reactions or more chronic conditions where they won't react in that four-hour observation period of your food challenge.

(Slide.)

DR. WOOD: You are going to hear more about food challenges this afternoon, but I will just mention a couple of issues here in terms of the way that they can be done. They can be broken down as open challenges where both the patient and the person administering the challenge knows what is being given.

A single-blind challenge is where the patient is blinded but the person administering the challenge knows the food that is being administered, whereas a double-blind,

placebo-controlled challenge is regarded as the most accurate test because it eliminates the bias that may occur on the part of both the patient, who may be feeling a great deal of anxiety about this food challenge, or on the part of the observer, who may have their own biases about this patient's allergy and might overinterpret or underinterpret symptoms.

We would say that these are going to be the most accurate tests for the diagnosis of food allergy. We would use them, if the history and lab results don't provide a clear diagnosis. That is often the case, again, when we have both a history that may not be accurate and laboratory tests that may not be completely accurate.

Then, we also do them very commonly to determine when an allergy has been outgrown. This would be a patient who has been known to be allergic to a food, and we would be monitoring them with some regularity in determining at some point that it is worth trying to retry that food.

We would typically do it in a controlled

setting, just because even in some patients you don't expect to react at all there may be significant reaction. Consequently, we have to do these with considerable caution.

(Slide.)

DR. WOOD: I think I pretty much mentioned this.

(Slide.)

DR. WOOD: Now, they asked me to mention, briefly, a study that we published last year looking at the risk of oral food challenges. What we have presented in this paper were results on almost 600 challenges, 253 of which were failed challenges. The patients reacted in the challenge, so that is where we can look at the risk. The other 57 percent, the patients had no symptoms, so it was a risk-free challenge once they might have gotten over the anxiety of being there.

We collected a lot of information on demographics, other atopic disease, symptoms during challenges, treatment needed, doses at which reactions occurred. Even though there is a lot

said about safety of food challenges, there has been very little published before this paper on what really occurs.

Now, I'm going to say this again a couple of times looking at the data, but I will say it up front here, that these results are not representative of the general population of food allergy.

These patients that are being challenged in this either had an unclear diagnosis, so it wasn't a dramatic kind of situation, or they were thought to have potentially outgrown their allergy and were being challenged to potentially prove that their allergy was gone.

We are really looking at very low-risk population, and it is not representative of the whole population of food allergy patients that are out there. Again, I will say this a couple more times looking at the specific data.

(Slide.)

DR. WOOD: Now, whenever we are doing this sort of analysis, we try to break things into

categories. One of the tough categories to decide is how do you rate reactions. You will see in the literature some different definitions that have been used.

We chose to create our own for a series of studies that we were doing, and talked about mild reactions that were skin and/or oral symptoms only. Oral symptoms is just at itching or they will often have an obvious hive-like reaction in their mouth or pharynx when they are having one of these localized reactions.

A "moderate reaction" was described as upper respiratory and or GI symptoms only or any three systems. When we are talking about systems, we broke that into: skin, GI, upper respiratory, lower respiratory and cardiovascular.

Then, severe reactions were those that were that were potentially life threatening, where they have lower respiratory and/or cardiovascular symptoms or any four systems were involved.

(Slide.)

DR. WOOD: When we broke things down into

these different systems which were involved in which challenges, you will see here that when we look at this column on the right here, which is the total in this paper we reported on milk, egg, peanut, soy and wheat.

The greatest number of failed challenges was to milk, 90; 56 to egg; 71 to peanut; 21 to soy; 15 to wheat; for a total of 253. You will see that skin manifestations were most common, 78 percent.

This is actually similar to what we have seen and what is in the literature in terms of reactions that happen out in the real world. Eighty percent of food reactions, 80 percent of anaphylactic reactions involve the skin, but about 20 percent do not.

Oral symptoms occurred in about a quarter, upper respiratory in a quarter, lower respiratory in about a third, GI in 43 percent. We, thankfully, had no cardiovascular reactions in this population.

Now, why would that be the case? It would

be for two reasons. The biggest reason is that cardiovascular reactions are not that common in children.

The cardiovascular system of a child is really sturdy enough to put up with the insult of an allergic reaction without necessarily becoming involved. Cardiovascular reactions are much more common in adults, and this population was entirely childhood.

The other reason that we might have seen the absence of cardiovascular reactions would be that we were dealing with a relatively low-risk population.

When we break it down into those three severity classifications -- mild, moderate and severe -- you will see that the numbers are relatively similar for each food. When we look at the total category, they broke pretty close to a third in mild, a third in moderate, and a third in severe.

When you look across the specific foods, the most important point that came out of this is

that you can't say that one type of food allergy in this kind of setting is more dangerous than another.

It turned out that the greatest number of severe reactions occurred with egg challenges. This was important information we thought to get out to get out to people doing challenges.

A lot of allergists will say, "I'm going refer you, Dr. Wood, all of my peanut challenges. I'm not touching a peanut challenge because they are really dangerous. However, I will do egg and milk challenges out in my office any time."

The message there is that really all of these foods have a potential to have severe reactions and need to be done in a setting where you are really equipped to deal with that potential for a severe reaction.

(Slide.)

DR. WOOD: When we looked at the RAST test score or the median IgE level for these different challenge results, we found that there was really no strong association between their IgE level and

the reaction severity.

Now, this is an example of where this population is not a good one to look at for this data. The reason is that we were essentially only challenging people that had relatively or very low levels.

We were not challenging people with very high levels where they were extremely likely to fail the challenge. There is no reason in most instances to prove that they are allergic. When you know with, say, 99 percent certainty that they are allergic, we would not put that patient through a challenge.

Consequently, if you went out in the real world where the RAST test levels range anywhere from zero to 100, you would typically see escalating reaction severity with levels that are higher. We have that data for peanut allergy where the group of patients that had levels at 100 did have more severe reactions when they had accidental exposures.

(Slide.)

DR. WOOD: Then, I think the last thing to present from this study is whether reaction severity was correlated or related to the percent of food ingested in these challenges. It turns out, if anything, it is inversely correlated. The more severe reactions, and none of these were statistically significantly, but if you look at the general trends, you will see here that the more severe reactions occurred with milk and eggs.

As you can see, the severe reaction for milk is 15 percent and 30 percent for eggs. When you look at the total group here, 50 percent, 45 percent and 30 percent.

(Slide.)

DR. WOOD: What is the reason this happens? Does this make any sense at all? Do you have your more severe reactions with smaller exposures? The reason we think it happens is because it is just identifying the more reactive patients.

It is picking out those that even though our test scores said that they are not so allergic

that they should do this, it is picking out those that react more abruptly and have more severe symptoms early in the challenge just because they were higher risk patients.

Now, we have come up in our studies about some decision making about when we would do food challenges. This is purely for clinical purposes. These are for those reasons of when we are trying to decide if they are truly allergic or when we think that the food allergy might have been outgrown.

What we would say is that we would do food challenges based on their history of reactions. If they have reacted recently, we wouldn't feel the need to do a food challenge.

We would base it on their laboratory testing, the skin testing and the RAST testing. Then he would base it on the importance of the food to the diet. There are some foods that are obviously much more important to the diet.

A family may never care whether that child ever eats a pea again the rest of their life. They

may elect to never have a pea challenge done, but they may be jumping to do a milk or what challenge at the first opportunity, because milk or wheat back in the diet would make such a dramatic difference in their day-to-day life.

Then, we have come up with some recommendations based on RAST testing of when we would recommend doing challenges. These cutoffs for milk, egg and peanut are all where we found a greater than 50 percent chance of passing the challenge, if you have levels below that range. For other foods, it has been harder to determine cutoffs, and we would challenge at higher levels for things like wheat and soy.

(Slide.)

DR. WOOD: Just to go through an algorithm of how we approach diagnosis, then, because it does impact on the discussions that are going to happen here, we would first take our history.

Based on the history, we would make some distinction whether we think this is consistent with an IgE type reaction or whether we think that

it is consistent with a non-IgE type reaction.

If it is IgE-mediated in all likelihood, then a skin test or a RAST test will help identify whether that food that was suspected to cause a reaction probably did or probably didn't.

If the test is negative, because the negative predictive accuracy is so high, we would feel that you could stop worrying about that food at that time. If the skin test is positive, because there are false-positive tests that occur, we need to do something more.

We might do a trial on an elimination diet; we might do a food challenge in one order or the other; and based on all of that information, we would arrive on the specific elimination diet recommended for that patient.

If it falls into a non-IgE category, the situation is much more difficult because we can't rely on a simple screening test to weed out those patients.

They are going to need some combination of challenges -- endoscopy, if it is a

gastrointestinal symptom; elimination diets, rechallenges, maybe a reendoscopy -- so there is a much more difficult plan on this side of the screen to sort out those patients.

(Slide.)

DR. WOOD: Now, I'm going to finish here with a couple of conclusions and present a couple of dilemmas. The conclusions are that food allergy is very common. This is a remarkably worthwhile initiative that is going on here, and that right now avoidance is the only treatment plan.

We really hope in the next 5 or 10 years that there are going to be other treatments for food allergy. It may be enough so that even if they don't cure the disease, that they will elevate the threshold to a point that we don't even need to have these meetings, that small exposures won't even be relevant. We are not even close to their yet, so avoidance is the only option.

Strict avoidance is essential to prevent reactions obviously, but we also think that in many patients it also helps to promote the outgrowing

process.

Here is where we may have very different thresholds. We may have a threshold that this child, say, with milk allergy -- they know for a fact that they can eat this bread that has whey as the tenth ingredient and never have a symptom. They are perfectly fine with it.

What we have found that getting that bread on a regular basis may keep their immune system more revved up to maintain the allergy so this thing that is way below their threshold for reacting acutely may still drive the immune system to maintain the allergy and prevent them from outgrowing the allergy.

The next conclusion is that food challenges are a useful means to diagnose food allergy and a useful means to determine threshold doses. There are going to be some limitations of challenges, and one of them is that as opposed to the study that I presented that Dr. Perry did with me, you have to include in a threshold type study the most allergic patients.

Doing the kind of patients that we are studying on the lower end of the spectrum has nothing to do with thresholds. It is irrelevant data. You can't go to my study and say, "This looks like a threshold because we are not including in those kinds of studies those highly allergic patients."

The greater dilemma, and this one is solvable, there are plenty of real allergic patients out there. They won't necessarily want to undergo these studies, because it is not a pleasant thing to have allergic reactions, but that part is potentially solvable.

The more difficult thing is a determination of the threshold doses that I mentioned for the chronic allergic conditions, especially those that are not IgE mediated probably isn't possible.

To give a couple of examples, if we take, say, milk allergy, the most common food allergy of all, and we are talking about an infant who is on a formula, there are a bunch of different options we

could have. Some of them can have soy, but some of them are also allergic to soy.

Some would go on to a formula like Alimentum or Nutramigen, which is a formula where the milk protein has hydrolyzed to a small enough fragment that in 98 or 99 percent of kids with milk allergy. It completely solves the problem. They don't react at all to that level or that type of protein that remains in that formula.

That other 2 percent, though, may react severely to that. They are typically the patients with the gastrointestinal disease. They are typically very sick; they are typically not growing; they are typically malnourished.

They are a group of patients who aren't at risk for the acute dangerous reactions, but they may be at very high risk for chronic disease from their food allergy.

Those patients will typically respond dramatically to a formula that is based in a single amino acids as a protein source, and that is a formula like Neocate and Elecare.

Now, when you take that population, and this is what I deal with every day, there is going to be a group of them -- and that is probably even less than 1 or 2 percent, it is probably only 1 out of 500 -- who still react to the Neocate. They can react severely to it.

We know that because of their gastrointestinal biopsies, their biopsies that are taken from their esophagus or stomach or intestinal tract still show evidence of severe allergy.

What we think those patients are reacting to would be either the absolutely trivial amounts of, say, soy protein that is in the soy lecithin, that is the eighteenth ingredient in Neocate, or the trivial, trivial amounts of protein that may be left in the safflower oil that is used as a fat component of Neocate.

When we switched those patients off of Neocate we can prove, and we have 15 patients now who we have proven, that taking them off Neocate resolved their food allergy. In this supposedly non-allergenic formula, they were still reacting.

Now, whether the direction this Committee needs to focus on is this very unusual patient or not is sort of a separate debate all together, but it is safe to say that there are going to be patients out there who break all rules. No matter what rules are established, there will be patients who completely break them and make all of our lives difficult from that standpoint.

I would be delighted to take any questions from the Committee or otherwise. Thank you for your attention.

CHAIRMAN DURST: Thank you, Dr. Wood.

Are there questions for discussion?

Suzanne.

QUESTION-AND-ANSWER SESSION

DR. TEUBER: This is Suzanne Teuber. I had a question about your patients with the Neocate sensitivity in terms of what the company reported for the soy lecithin, did they have any values that you could report back as to a chronic ingestion threshold?

DR. WOOD: No. I mean, most of these kids

it is most likely the soy lecithin. SHS doesn't have that data on the protein content of their soy lecithin. They say it is zero. These kids when they were switched to Neocate One Plus, which has no soy lecithin, their disease went away. We have to assume that there was enough there to drive that process.

CHAIRMAN DURST: Yes.

MS. HALLORAN: Jean Halloran. Could you say something about the process about growing allergies? How does that work? What actually happens?

DR. WOOD: Well, that is a very good question. There are a number of things that we don't understand too well. However, what we think is that in the majority of patients we think that outgrowing is most related to the immune system gradually forgetting about that concern that it earlier had.

That is where we think that strict avoidance is likely to promote the outgrowing process, and with a prolonged period of strict

avoidance for many of these foods, the immune system has a memory that isn't long enough to maintain the allergy and that it will gradually wane and then full tolerance will be accomplished. There are probably lots of other mechanisms going on immunologically that are not well understood.

The other question with this that we have no great explanations for, lots of theories but no great explanations, is why you can take a food allergy like milk, which in early infancy can be every bit as severe as a peanut allergy, and have most kids outgrow that allergy, while very few kids outgrow the peanut allergies. There is something very different about the immunologic memory of one food allergen versus another.

CHAIRMAN DURST: Yes.

DR. KELLY: Ciaran Kelly. I wanted to come back to the issue of challenging individuals with severe allergies as a method for determining a threshold. I would like to hear your comments as regards the feasibility and safety and whether that would be ethical to perform? I guess my concern is

that once the threshold is crossed, whatever that threshold might be, isn't there a potential for severe allergic reaction?

DR. KELLY: Yes. Absolutely. There have been threshold studies done for the biggie, peanut, with very allergic people so it is doable. Now, what we can say about this is that these studies won't be done in children. It is not going to happen.

That automatically limits your population of people, because when you go out and try to find your group of milk-allergic adults to do these studies on, you are limited.

Now, they do tend to be more severe reactors. From that standpoint, you have some patients out there, but there is no IRB that is going to let us do this in children. There has to be demonstrated benefit to do a study with risk.

The safety element is one that we are comfortable with, recognizing that you need to have emergency management available to you because there will be people that have bad reactions.

The safety that is built into that is starting with exquisitely small doses and working up very gradually and aborting the challenge whenever you see your first symptom.

That may lead you to end some challenges prematurely. You may end up with a false threshold, but you are obligated to stop when you have objective signs that patient is reacting.

The ethics beyond that to me is that if it is an adult patient who is willing to consent to that process, I have no problem with the ethics of doing it and have no fear that I will ever lose a patient to a food challenge.

CHAIRMAN DURST: Yes.

DR. BRITTAIN: This is Erica Brittain. Since you can't study children in that way, do you know how this threshold might be different in children, if you've got the threshold for adults?

CHAIRMAN DURST: No, we don't know that. That data is, to my knowledge, not available in a large enough sample to have any validity whatsoever. It is a superb question. The argument

is going to be and will always be these children are much more reactive than the adults for most of these foods.

For peanut allergy it is going to be the simplest, because allergy tends to persist. We think that people usually hit their peak level of severity as an adolescent or young adult, so that would be fairly easy to solve.

However, when you look at the others like milk and egg and soy and wheat, you are by and large going to have the highest level of reactivity in your first couple of years of life.

When we think about those allergies, we usually think of growing into the allergy for one or two or three years where they are becoming more and more allergic, and then they are becoming less and less allergic over the next one or two or three or four or five years as they outgrow the allergy. It is a moving target at all points, but the most severe reactivity is likely to be early on.

CHAIRMAN DURST: Dr. Wood, I have a question -- this is Dick Durst -- just points of

clarification. On your slides where you indicated "wheat," now this is the IgE-mediated type allergy as opposed to our discussion tomorrow on celiac disease?

DR. WOOD: Yes, these results are entirely IgE.

CHAIRMAN DURST: Okay. Do other grains cause the IgE type reaction as the wheat?

DR. WOOD: Yes, our study there, about 600 challenges, came out of about 3,000 food challenges that we have done. There were five most common foods that I had enough data to make some conclusions that we were comfortable with. All of the grains cause allergic reactions.

It turns out that wheat and rye are very cross reactive from an IgE-mediated allergy standpoint, and that most patients allergic to wheat are also allergic to rye; it turns out that about half are allergic to barley; and 10 to 20 percent are allergic to oat. Beyond those grains, all of the other grains and grain substitutes are clearly capable of causing allergy in select

patients.

CHAIRMAN DURST: Thank you. One other question as far as clarification at least for my mind. One of your slides with the food challenge decision making had the units in caps "KU/L." I don't know if you defined that? I was curious.

DR. WOOD: Yes. It stands for "kilo unit" of IgE in a specific assay that Pharmacia has developed called an immunoCAP RAST. It all goes back to this one technology that is thought to be the most accurate quantitative measure of specific IgE, and the results are represented in that kilo unit of IgE, the specific IgE antibody per liter of serum.

CHAIRMAN DURST: Thank you.

There is another question?

DR. KELLY: I have one other question. Dr. Wood, you made a very important comment about the potential for continued subclinical exposure to allergens perpetuating an allergic response. How well accepted and how well documented is that, or is that largely a clinical impression?

DR. WOOD: Very well accepted, very poorly documented. It is widely accepted. There is very poor information to support it. There are only a couple of studies. The problem we have is we tried to do the study, and we were turned down because it is so widely accepted that to go to the IRB and propose to them that we are going to take this group of kids with milk allergy and keep them on low-dose milk and take this group and have them strictly avoid it was turned down.

Now, there is some work being done that has identified instead of looking at the IgE against milk globally, it has turned out that if you have IgE against certain portions of the milk molecule it may be more predictive of a longer-term allergy, and if you have it toward others, other epitopes, it may be more predictive of an allergy that is easier to lose.

We think that it may be feasible to focus on that population that has a very good chance of losing their allergy, even if we make a mistake, to be able to do this study. It is doable, but the

outcome is about 10 years down.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: I have had some experience --

CHAIRMAN DURST: Identify yourself.

DR. SILVERSTEIN: Marc Silverstein, Baylor Health Care System in Dallas. I have had some experience in studying the epidemiology of asthma and anaphylaxis. In both of those conditions, your findings are very much dependent upon your diagnostic criteria.

In clinical medicine, we have diagnostic criteria. You have described the criteria for food allergy, which would involve components of: history, physical exam, laboratory tests, food challenge, and response to clinical management with elimination diets.

Are there standardized criteria that you would see moving the diagnostic criteria that you would use from clinical practice to investigation and publication in peer review literature and/or perhaps the policy in making regulatory decisions?

I am interested in, Is there a set of standardized criteria that professional organizations or clinicians would use for investigation or for recommending policy? I understand there is some recent work on definitions and standards for anaphylaxis?

DR. WOOD: The definitions for IgE-mediated food allergy are pretty clear and it is pretty well accepted that it is if you have a history that is consistent, you have a positive allergy test, and you either fail a challenge test or pass a challenge with a dose that is generally accepted to indicate full tolerance. It is fairly straightforward and well accepted in the peer review literature.

It is much more difficult on the group of patients with, say, eosinophilic gastroenteritis where they don't necessarily have IgE. You require a histologic diagnosis to identify the condition, and then figuring out whether they have food allergy driving the process exclusively, partially or not at all is a much more difficult process.

It is doable, but you have to eliminate foods, rebiopsy, reintroduce foods, and rebiopsy. There are studies that have done that, but it is so much more difficult to do that there is much less of an acceptance of an absolute diagnostic criteria, much, much less.

It is being looked at. This is a form of allergy that is clearly either happening much more often or being identified much more often or both, so that the potential is there, but it is much further away from a definition that is well agreed upon.

CHAIRMAN DURST: Yes.

DR. BRITTAIN: This is Erica Brittain. I have a clarification question on the food challenge. How is the placebo control implemented?

DR. WOOD: I think you are going to hear a lot more about food challenges this afternoon, but the idea, and it is going to vary depending on the age of the patient and what they can do, but the idea that it needs to be well disguised and obviously safe from the perspective of that

patient's allergen --

(Simultaneous discussion.)

DR. BRITTAIN: But --

DR. WOOD: Go ahead.

DR. BRITTAIN: I'm sorry. Is it by a dose? Is a particular dose placebo, or does a patient get all placebo?

DR. WOOD: Yes. I'm sorry I misunderstood. The normal way the challenge is done is to have a separate challenge for the placebo and for the actual food being studied. The usual way it is done is that the patient would come in and have a day doing a placebo challenge and come in and have a day doing the food challenge.

Challenges can be done in a matter of a couple of hours in some situations, but to do highly allergic people in a placebo-controlled manner would usually take 8 or 10 hours for each day.

CHAIRMAN DURST: All right. Seeing no further hands in the air, I think we will thank Dr. Wood. We are right on schedule. Thanks again.

Our next speaker will be Anne Munoz-Furlong, who is director of the Food Allergy and Anaphylaxis Network, who will discuss patient perspectives on food allergies.

PATIENT PERSPECTIVES ON FOOD ALLERGIES

MS. MUNOZ-FURLONG: Thank you. I would like to thank the organizers of the meeting for the opportunity to be here.

(Slide.)

MS. MUNOZ-FURLONG: What I would like to do is in that time that I have been allotted is give you a sense of who this food allergic consumer is; the food allergen labeling from their perspective; and then, most importantly, their way of looking at threshold levels for food allergens.

(Slide.)

MS. MUNOZ-FURLONG: By way of background, the Food Allergy & Anaphylaxis Network or "FAAN" is a non-profit organization. We were established in 1991 and have 27,000 members, almost 28,000 members. Eighty percent of these people come to us from physician referrals, so we know we are talking

about IgE-mediated responses when we are looking at our membership.

Our mission has four points: to increase public awareness, provide advocacy and education, and advance research on behalf of those with food allergy.

(Slide.)

MS. MUNOZ-FURLONG: Now, as Dr. Wood said, food allergy is believed to affect about 11 million Americans or 4 percent of the population; fish and shellfish allergy, 2.3 percent or 6.5 million; individuals in peanut and tree nut, 3 million.

Consequently, between these four foods we are talking about almost 10 million Americans. These are the four foods, as was presented earlier, that are lifetime allergies and also are believed to cause the majority of the severe or fatal reactions in this country.

The other point I want to make here is that although we are talking about 11 million patients, our data shows us over and over again that most of these patients have families who

follow their restricted diet. The impact is actually many times greater than the number of patients.

(Slide.)

MS. MUNOZ-FURLONG: When we look at shellfish allergy, this is looking at data that we published about a year ago now. Te prevalence of shellfish, we found about 2 percent of the population or 6 million Americans.

The key foods responsible for the majority of these reactions in rank order are: shrimp, crab, lobster, and clam. For fish allergy, .4 percent of the population: salmon, tuna, catfish, and cod being the primary fish that cause reactions.

However, if you look at these a different way, these foods, especially shrimp or salmon, are available on almost every menu that you are going to look at in a restaurant or food service establishment. Therefore, the risk for these individuals is constant.

(Slide.)

MS. MUNOZ-FURLONG: Talking about tree

nuts, and these most of you already know, are not peanuts; they are different. Most people with a peanut allergy avoid tree nuts as a precaution but not because they are allergic to them. About 20 percent of the 20 peanut allergic population is allergic to tree nuts as well.

When we are talking about tree nuts, it affects about 1.5 million Americans. Again, looking at data from our patient registry of 5,000 patients, we find that walnut, cashew, almond and pecan are the leading cause of tree-nut-allergic reactions in this country.

(Slide.)

MS. MUNOZ-FURLONG: What does it mean to have food allergies? It is vigilant label reading. You have got to read labels not just for food ingredients but anything coming into the home. Bath products can have tree nuts, milk or eggs in them, for example.

Pet food, if you have ever looked at the ingredient statement on a pet food, it can have almost every single one of the major eight

allergens.

That is something you have to worry about, especially if you have a toddler who will pick up food from the floor or anyplace else they can get it. Also, medications have been known to have allergens in them, particularly milk.

It is not just a question of label reading for food; it is for anything. Trace amounts can cause an allergic reaction, and that has been proven over and over again.

Just one bite can cause a reaction. Therefore, we can't tell by looking at someone how allergic they are going to be or what their tolerance will be to that food.

Currently, as Dr. Woods said, the only cure now is a dose of epinephrine, if the patient has a history of severe reaction. The onus is on the patient or the family to read the label and avoid the allergen and then be quickly prepared to handle an allergic reaction, if they have made a mistake or accidentally ingested the food to which they are allergic.

(Slide.)

MS. MUNOZ-FURLONG: Because there is no cure, decisions about any part of the person's life are centered around food allergy. This is what makes food allergy so stressful on the family and on the patients.

Whereas with other allergies you have seasonal components and you might have an easy spring but fall is the bad season or if you are allergic to cats or dogs you can avoid those, with a food allergy every decision every single day is affected by your food allergy.

Food shopping can take two to three to hours just from reading labels. Cooking, if the family is bringing the allergen into the home, they then have to prepare two meals, the non-allergen-containing meal and then the allergen-containing meal, and take precautions to avoid cross-contact.

Decisions about dining out and socializing are made based on not a food preference, but is the food safe.

"Can the manager be trusted to give us accurate information?"

"Can the person we are visiting be trusted not to slip some of the allergen into the food?"

Then, the decision is made to move forward based on the answers to those questions.

Even what school or childcare the individual will be sending their food allergic child to are going to first be centered on food safety from a food allergy perspective.

Vacation and travel where you and I might decide whether we want to go someplace warm or go skiing in the winter, these families have to think first about food.

"Can we ship food there?"

"Is there a safe place?"

"Can we rent a room with a kitchenette and make some of the meals so that we can maintain some level of safety?"

Even family relationships, there is always somebody in the family that does not believe the food allergy is real, and so decisions are made

about whether they can visit that individual or not.

(Slide.)

MS. MUNOZ-FURLONG: As a result of all of this, it has a tremendous impact on quality of life. We published a study several years ago looking at the impact of food allergy on quality of life.

What we found is that families who have a food-allergic child score lower on their perception of whether their child has good health or not, the emotional health and family activities than the general population.

Certainly, they scored lower or worse than families who are looking at or dealing with other chronic diseases such as diabetes, juvenile, rheumatoid arthritis and attention deficit disorder, for example.

We also looked at some of the other influences. If the individual has a food allergy and asthma or atopic dermatitis, that further lowers their score for the quality of life.

If a family has a child with two or more food allergies, that group scored much lower in 9 out of 12 scales compared to those who only have one or two food allergies that they are dealing with.

When we look at our patient population at FAAN, we see that it is not uncommon for our members to report a child with a milk, egg and peanut allergy simultaneously. You can imagine eliminating those three foods and how it compares to the impact on the quality of life for the entire family.

(Slide.)

MS. MUNOZ-FURLONG: This is how, again looking at the same data, you can see here in blue is "General health" perception. Food allergy lower than the normal for asthma, attention deficit disorder and some of these other symptom scores.

Now, in talking about label reading, which is really the cornerstone of managing a food allergy. Here is what goes on.

(Slide.)

MS. MUNOZ-FURLONG: The person with a food allergy is told by the physician, as you heard earlier from Dr. Wood, "You have an allergy, avoid the food." Zero tolerance. They must live in a black-and-white world. If you are allergic, you don't eat that product.

If the allergen is listed on the label or the label says "Contains allergen," they are not going to eat that product because they are trying to avoid a reaction. As a result, they expect ingredient labels to be consistent and, most of all, reliable because this is what they are basing the decision about food on. It will affect their health and safety.

When they see the same product with different ingredient statements, it makes them very confused and frustrated and sometimes very nervous because they, again, are looking for consistency in labeling.

What we are already seeing with some of the companies complying with FALCPA regulations is that there are products on the market that are

pre-FALCPA and FALCPA compliant with different ingredient information regarding allergens. Already we are getting calls from our members.

"Which one of these labels is correct?"

"What if I hadn't picked up that second label? How would I have known?"

This is what we are heading into as we start to change these labels.

(Slide.)

MS. MUNOZ-FURLONG: The challenge for food-allergic individuals is that the patients are told to strictly avoid the allergen, there is zero tolerance or be prepared to handle an allergic reaction. Once a reaction begins, we don't know how severe that is going to be.

They are not aware that there are scientific names to foods when they are newly diagnosed. This is something FAAN spends a lot of time doing. It will get better as FALCPA is implemented because labels will have simple ingredient terms on them.

We have to remember it is not just the

patient or the patient's family reading the label, but it is the teacher, the scout leader, the friends and family members. The impact for any labeling decisions are going to be quite broad.

(Slide.)

MS. MUNOZ-FURLONG: Allergens can appear in unexpected places. This is just one slide of a number of examples that we have for "Common Foods in Unexpected Places." Every one of these examples have caused an allergic reaction to one of our members, because they were not expecting to find the allergen.

Just to give you an example, if you have a milk allergy, you would not have expected that barbecue-flavored potato crisps might have milk in them, and you might not have read that label, or that canned tuna might have soy in it. Therefore, it is not as easy as avoid the food, you've got to be looking for unexpected sources.

(Slide.)

MS. MUNOZ-FURLONG: We can see this reflected in a study that was published in 2002 by

Joshi, et al. They took some food-allergic individuals, gave them products that were on the market, and asked them to read the label for the food they were trying to avoid.

You can see here that families avoiding milk, only 7 percent were able to accurately identify milk on the labels that were presented to them; for soy, they did a little better at 22 percent; but peanut, only 54 percent got the label reading correct, and most of this was because of confusion about allergen labeling information.

(Slide.)

MS. MUNOZ-FURLONG: The problem with allergen labeling information, there are no guidelines or standards for use. This is completely voluntary. As a result, every company has their own decision tree and algorithm and wording for what terms they will use and under what conditions.

This makes it very difficult for us to educate consumers and the others who are reading labels on their behalf and telling them what to do

and what these mean.

The proliferation of "may contain" labeling has really caused us some problems. Just to give you a sense of what is going on, we had one volunteer go out in the Northern Virginia area to one grocery store and look at products from cookies, crackers, candy and bakery. We were trying to follow the model of a previous FDA study.

She came back with 28 different versions of "may contain" statements. From the consumer's perspective, what does that mean? Can they be trusted, or should we ignore them?

(Slide.)

MS. MUNOZ-FURLONG: The current environment because of this, there are some physicians that advise their patients to ignore precautionary labeling, because it is everywhere and there wouldn't be any food for them to eat.

There are others who tell them, "Heed the warning and avoid those foods."

Then, there are some companies who tell the consumers, "It is on the package only because

our legal counsel has advised us to put this on there."

Then, there are others that say, "You have to trust that wording and not go near the product."

How does a consumer determine which is which?

We are also seeing advisory statements for peanut allergy only. The way the consumer interprets these statements is that they are shortcuts to label reading.

If they see "contains peanuts" or "may contain peanut," they may not read the rest of the ingredient declaration if they are looking for milk or soy, because they think that the company understands food allergy and would have listed all of the allergens on there.

As a result of all of this, consumers are confused and frustrated. Particularly what is going on as their food choices are further minimized is that there is risk taking behavior by parents of kids with food allergies who decide, seemingly randomly to us, that some companies can

be trusted and others not, so they will ignore "may contain" on the companies they trust.

Then, the teenagers, our highest-risk population for a severe reaction, want to be like everyone else are reporting that they are ignoring "may contain" statements, because it is on so many foods they have eaten the food and not had a reaction, so they don't really believe that these are true.

(Slide.)

MS. MUNOZ-FURLONG: This is one of the labeling studies that we conducted with our FAAN members during a spring meeting a year or two ago. We asked a question. They were supposed to answer, "I would never purchase a product that says it contains" whatever the "allergen" is. You can see that almost 100 percent of them would avoid a contain statement.

However, as you go from very specific to black-and-white to vague "packaged in a facility that also produces," say, peanuts or nuts or whatever the allergen might be, only 74 percent

would avoid purchasing that product.

Consequently, 25 percent of the allergic consumers are going to purchase products where they don't really understand the precautionary labeling. If the company is putting this on here because of some risk, we've got a miscommunication or a communication gap going on.

(Slide.)

MS. MUNOZ-FURLONG: Let's talk about thresholds, then. Again, from the consumer's perspective, their physicians advise, as you heard from Dr. Wood, is strict avoidance or a reaction may occur and you will not outgrow this allergen. They are very motivated to try to strictly avoid that food.

When we talk about thresholds to our members, and these tend to be the most motivated and well-educated of the food allergy population, this is what we consistently get back. They believe that threshold levels may put their children at risk because their child is so allergic.

They also wonder whether the threshold levels, the whole discussion is based on the industry or the government trying to figure out a way not to have to clean or label for allergens. Again, they are wary that this might be a loophole that is trying to be directed at them.

(Slide.)

MS. MUNOZ-FURLONG: The catch 22 here, from where we are at FAAN, is that we understand that if we label for all allergens at all levels it will further restrict diets. If we further restrict the diet, we are going to increase frustration which will yield risk taking.

It is going to undermine the integrity of the ingredient label. As I showed already with "may contain," we are already seeing that. They believe "contains." However, if we put "contains" on everything and they eat it and don't have a reaction, we are going to diminish the validity of that statement.

If we undermine the integrity of the ingredient label this will potentially lead to more

allergic reactions as they take more risk, which is going to increase the number of doctor visits; hospital visits; and, potentially, fatalities.

(Slide.)

MS. MUNOZ-FURLONG: Here is an example of what can go on and what we see as what we may all be facing. This is a report that came to us from one of our members who had a soy-allergic child who had safely eaten soy lecithin in the past. Most of our members, although we tell them to read the ingredient declaration on products every time they purchase them, become brand dependent and stop reading the ingredient label. That is exactly what happened here.

This was a product that the child had safely eaten in the past. The mother did not read the label, gave it to the child, he started eating it. She then started reading the label and saw that it now says "contains soy." She got very nervous and screamed that it contained soy and asked the child to spit the food out.

Immediately, he started having itching,

leading to hives, and a feeling of impending doom. The mother gave him medication and thought she was having a full-blown reaction.

The question we have to ask ourselves, Was this a reaction, or was it a panic attack? She called the manufacturer and was told that the "contains soy" is because it contains soy lecithin. Therefore, the ingredients hadn't really changed from the product that they had safely eaten before.

From our perspective, we do not want to see consumers or their families subjected to this kind of fear. Because what you don't realize is that once this reaction is taken care of, it takes a long time for the family to trust again. We do have reports of children developing eating disorders and just being very cautious about being around other people once they have had a reaction.

(Slide.)

MS. MUNOZ-FURLONG: From the consumer's perspective, if we are looking at developing a threshold level, and as I said there are pros and cons to both sides of this issue, the key here is

we have got to do a good job of education. We have got to educate physicians and registered dieticians so that they can counsel patients accurately.

As you saw, we have done no training for "may contain." We have got some doctors that say, "Just ignore it." We can't afford to do that with threshold levels.

We also have to educate patients and their families and assure them that the food is still safe and that they can trust the information on the label. We also have to do outreach to the food industry so that they can answer the queries from food-allergic consumers in a way that will give them confidence instead of make them nervous or suspicious about whether they can trust the information on the label.

(Slide.)

MS. MUNOZ-FURLONG: In summary, food-allergic consumers want as many food choices as safely possible. This is really why we are here and why we are seeing some of this behavior with advisory statements.

They want to open the diet. The children want to be like everyone else, and they want the least amount of restrictions, but they need to be safe.

The consumer needs to understand the information on the ingredient statement. They need most of all to trust that that information is reliable and it is going to be consistent from one product to the other. They also need a minimal number of precautionary allergen statements and a guideline so that they understand what these statements mean and what they should do as a result when they see these on products.

(Slide.)

MS. MUNOZ-FURLONG: In conclusion, the current labeling and manufacturing practices present enormous challenges to food-allergic consumers. As Dr. Wood said, the number of these patients is increasing.

To give you an example, we conducted a prevalence study of peanut and tree nut allergy in 1997, repeated that same study in 2002, and found

that in that five-year period the number of children with peanut allergy had doubled. We don't know how it is continuing to trend, but reports are that it is still increasing.

(Slide.)

MS. MUNOZ-FURLONG: The bottom line is above all we must protect the integrity of the ingredient information. Because from the food-allergic consumer's perspective, they depend on this information to avoid an allergic reaction and, most of all, to maintain their health and safety. We already have data showing that food allergy impacts the quality of life. We don't want to further diminish their quality of life.

With that, I will end here and open for questions.

CHAIRMAN DURST: Thank you.

Does the Committee have any questions?

Yes.

MS. HALLORAN: I mean, obviously a person can survive without ever having to buy any packaged food. I am wondering in terms of the kinds of

things you were talking about -- teenager's preferences, the needs of a busy mother, et cetera -- are there particular categories of food that are prepared and packaged that are most sort of important and essential in our modern life? I mean, would it be bread or breakfast cereal or--?

MS. MUNOZ-FURLONG: If they ate vegetables, they would be fine. How many kids want to eat vegetables?

(General laughter.)

MS. MUNOZ-FURLONG: I think it really goes back to quality of life. Children want to be like everyone else, and they will do everything they can to fit that mold.

I have a daughter that was diagnosed with milk allergy and egg allergy when she was an infant. I will tell you that I did everything I could to make sure that she felt like her friends.

It is not just the patient or the child, it is also the family wanting to not have their child isolated or feel stigmatized because of the allergy.

If everyone else is having breakfast in a box, that is what these kids want. What we want is to make sure that those labels are accurate, if the family makes that decision.

Granted, there are some families that are very cautious and will only make food from home, make it from scratch. However, as the child gets older and is out with friends, that is just not doable.

MS. HALLORAN: Are there any particular categories of foods?

MS. MUNOZ-FURLONG: No. As you saw in that slide, "Common Foods In Unexpected Places," we are seeing allergens everywhere. We have just got to make sure that all of the labels are correct and can be trusted.

CHAIRMAN DURST: Yes.

DR. KELLY: Ciaran Kelly. A question for you from your perspective and the perspective of the people you represent, the patients with food allergies.

I understand that you are frustrated and

find it very difficult to work with the current system of many different types of wording. Would it be better for you to have a two-level system, "does not contain" and "may contain traces of" -- or even three levels, "contains" and "may contain traces of" and "does not contain"? Would that be acceptable?

MS. MUNOZ-FURLONG: Well, I will start from the back end of your question. If you poll our members or just the general consumers, they all want "does not contain" labeling.

I would caution to you because of the reports I've seen. This is very widely used in the U.K., our colleagues in the U.K. have reported, recalls to products that say "does not contain peanuts" when they do contain peanuts undeclared.

From the way the consumer is going to behave if they see "does not contain," they may not read that ingredient declaration because that is the guarantee they have been waiting for.

I am not in favor of "does not contain." I am in favor of let's have them read the

ingredient declaration and know that they can trust if it doesn't have peanuts in that ingredient statement, the product should be safe for them.

When we start to see different allergen statements, we want to make sure that those can be trusted. When we are talking about "does not contain," that is an implied endorsement or guarantee, which makes me very worried. If the company makes a mistake and that is on the label in error, we could have someone pay for it by having a reaction.

Now, if we have two levels, "contains" and "may contain," as along as we know what that means and that all companies are following this guideline, that makes it much easier. Right now, you can go poll 12 companies and they each do different things.

CHAIRMAN DURST: I think we need to move on.

Thank you.

Our next speaker will be Susan Hefle, associate professor and co-director of the Food

Allergy Research and Resource Program at the University of Nebraska, who will be speaking on "Allergenicity: Analytical Methods."

Dr. Hefle?

ALLERGENICITY: ANALYTICAL METHODS

DR. HEFLE: Thank you, Chairman Durst.

Good morning. I am going to discuss the basic analytical methods for allergens. The model used is the ELISA-based model which has lateral flow. This model has been used for several years now. We will discuss this more later.

Our second bullet, the most successful kids do use polyclonal antibodies but occasionally a kit uses monoclonal antibodies directed against a single protein. Usually, the antibodies are directed against a crude extract of an allergenic food not the specific proteins themselves. It is not necessary to really measure the allergen.

The industry just cares if any peanut is there, not if one particular protein from a peanut is there. "Ara h 1" is a particular peanut allergen. The industry just wants to know if any

peanut or whichever peanut is there.

A lot of times a lot of the successful kids use a much more kind of crude approach to detecting peanut rather than specifically horning on the allergens themselves.

There is a challenge, though, in that different standards are used in the different kids, depending on the manufacturer, and also different antibodies are used in the different kids depending on the manufacturer. It is not like a standardized approach across the board, necessarily.

(Slide.)

DR. HEFLE: The detection limits range from around 0.1 to 2.5 parts per million for the quantitative methods. There are also quality methods; however, if we are talking about threshold levels, we need to talk about quantitation here.

Using a method that has a very low detection limit has certain challenges. Every kit has the ability to have a low detection limit. Ten years ago, when I started developing kits, Steve Taylor and I sat around and thought about