wheat-based and gluten has been removed but would contain up to 200 parts per million? I realize the numbers are in question.

MS. KANE: Right. They do not apply to the term. They don't want the term "gluten-free" to apply to naturally gluten-free foods but those that have been specially processed or prepared where the formulation has been controlled.

There is a substitution of ingredients or a removal of gluten from ingredients. It would cover categories that are wheat-starch-based. That is where the 200 parts per million definition is coming into play.

Member countries did not want wheat-starch-based products to be excluded from being called gluten-free, if there was only one definition of 20 parts per million. That is why they compromised and had the two levels that would apply.

DR. McBRIDE: A follow-up. Would I assume that they would then be called something different, or would we be expecting the consumer --

(Simultaneous discussion.)

MS. KANE: No. Right now, as it stands, they are saying one definition "gluten-free" to apply to three categories of gluten-free. However, that could change.

Now, keep in mind all of this is pending. It is at Step 7 of an 8-step process. I know there is a Working Group, the Prolamin Analysis and Toxicity Group. That information will come into play. These levels are not definite and they could change.

If both of those situations or all three were called gluten-free, then we would have to expect that the consumer who felt that they were very sensitive and wanted truly a very low level, below 20 parts per million, would have to read and understand the names for the various grains, et cetera, that would be on the ones where in fact products that at least one time had contained gluten were used.

I understand that, and the report I cited on my second slide, the "ALINORM Report" is the

latest one, to my knowledge, that contains the language of the current proposed standard at Step 7. It doesn't go into those details about how it might be labeled alternatively or what additional information it would include. You're right, it does create confusion. How would you know if it is 20 parts? How would you know if it is 200 parts?

That issue was brought up in some related documents, but it is not found in the latest session report. However, you're absolutely right.

DR. NELSON: This is Mark Nelson. I just want to address that question about the Codex label. There is a separate committee, Codex Committee on Food Labeling, and these definitions I would expect would ultimately be referred to the Codex Committee on Labeling to address the issue you have just raised about the potential confusion.

CHAIRMAN DURST: Suzanne.

DR. TEUBER: Suzanne Teuber. I also see an issue about cross-contamination problems with foods that you wouldn't expect to contain gluten

and yet might contain contaminants because some of these, the rules that you are talking about, really don't address that.

Do you have any information on that, like say, corn that may be processed in a place that also has processed wheat? It really would be beneficial to the consumer if it were to undergo testing and have a specific label, and yet these other definitions in other countries don't seem to cover that all. It would probably just come out with no statement. Is that a correct interpretation?

Or, actually maybe, Dr. Nelson--?

DR. NELSON: I think in Europe and Codex also has a standard for good manufacturing practices; the Europeans have the equivalent. I think the issue there would be the responsibility of the manufacturer to maintain good manufacturing practices and prevent as much possible that cross contact.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. Would

you clarify the categories of foods to which this would apply? I would like you to, because I'm not sure I understood the criteria exactly. If a food has multiple ingredients, does this apply to all of the ingredients in the food?

This is packaged and labeled food. One or the major ingredient may be a food which in its normal form does not contain gluten, yet there might be other ingredients perhaps mixed in with it that would.

Would it be that it applies to a labeled package food which any of the ingredients contain gluten, or would it be just the major ingredient does not contain gluten and there might be some additive or some other component ingredient?

MS. KANE: It is my understanding it would apply to all ingredients. It would be selectively. If a packaged food that is labeled gluten-free, it would have to conform to the proposed. Of course, again, it is proposed so it is not a done deal. However, there are categories going back.

Can we go back? Can you reverse it back.

It is probably more towards the front. Okay, that one right there.

(Slide.)

MS. KANE: That is the first category consisting of ingredients. It doesn't say primary ingredients. It means ingredients. That is how I understand it. Keep in mind I've never been a member of the U.S. delegation to a Codex Committee meeting. I do not have firsthand knowledge of the discussions. It is only based on my reading of their session reports and related documents. The way that is written I would interpret that to mean all ingredients. Maybe someone who has attended the Codex could speak to that?

CHAIRMAN DURST: Mark.

DR. NELSON: Mark Nelson. I think everybody would interpret that as all ingredients not just the main ingredients but including the minor ingredients, flavors, spices, and so on.

I can just talk a little bit about my experience in the food industry. I have worked both for packaged goods companies but also

suppliers to packaged goods companies.

They look at it very carefully to find out what the subingredients might be in, say, flavors or an additive or carriers or something like that. I can assure you, being a supplier to companies like Nestle or Kellogg's or Kraft, we have to provide a fairly substantial dossier to them for every ingredient we supply them to deal with issues like allergens and gluten levels as well. The food industry itself does take this very seriously.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. I guess this is more a question. It seems to me that based on what we have seen on some of the slides you've shown today that there really isn't good analytical method to be able to determine.

For example, the nitrogen content, you could measure every protein in there and you could weigh overestimate the amount of gluten. Measuring gluten in the insoluble water fraction, that seems to be, again, if you can solubilize it. If you can't really detect it, okay.

DR. NELSON: I'm sorry, you may have to start over. Sorry about that.

(General laughter.)

DR. MALEKI: It is kind of a question. Based on this, I don't think there is really an analytical method that can make you comply to this, so how does this work? How are they going to enforce it?

MS. KANE: Keep in mind that the nitrogen definition of gluten is the current one. They are proposing it be defined as the protein fraction for wheat, rye, barley, et cetera, to which persons are intolerant and it is insoluble in water and a 0.5 molar solution to sodium chloride.

However, there is an analytical method component of a standard, and that is pending because they were talking about the R5 Mendez method, ELISA. They knew that they would have to have a method that was sensitive enough, reliable, accurate and would detect the types of proteins that they are talking about in their definition.

That is going to be, I'm assuming, part of

the discussion at the next Codex meeting is to bring that information about the methodology into play, because those were the two components, the methodology and threshold levels. Those are the two areas needed to be worked out, and so I think that is going to be the crux of the discussion at the next Codex meeting.

DR. MALEKI: I just wanted to make a comment as a follow-up.

CHAIRMAN DURST: Oh, okay.

DR. MALEKI: I'm Soheila Maleki. It seems like the antibodies, the R5 kit again doesn't detect gluten it detects gliadin. Maybe Steve can help with that somewhere along the line.

All right, go ahead.

DR. CALLERY: Pat Callery. If the analytical part can be worked out, which I think it can. I wonder if there is an analogy here with caffeine where we have caffeine-free sodas and such, which we expect to have no caffeine, and coffee that is decaffeinated that does have caffeine in it. The word is not very pretty,

"deglutinated."

There may be an analogy that says when it is gluten-free it is truly gluten-free and when it is deglutinated, then there is a perhaps 20 parts per million or something, whatever the standard would be. That might be easier to understand.

CHAIRMAN DURST: Dick Durst. You mentioned that the next meeting is in November of this year. Do you get the sense that they will finalize the document at that point?

MS. KANE: Oh, I wouldn't venture to say that at all. I don't know, and I don't know how close. Again, I've never been involved in their meetings, and there is an eight-step process. They could go back and revisit the issues; they could go forward, and then it could advance. However, I don't have a clue.

DR. NELSON: This is Mark Nelson. Even if they did adopt it at the committee meeting, it would then have to be forwarded to the overarching body, which is the Codex Commission for them to adopt it, and that will be next July.

CHAIRMAN DURST: Thank you.

Any further discussion?

Jean.

MS. HALLORAN: I think everyone should realize that Codex standards are not biding on anybody.

CHAIRMAN DURST: Okay. Thank you, Rhonda.

MS. KANE: You're welcome.

CHAIRMAN DURST: We will take our lunch break. We are about 15 minutes over, but I think we have sufficient time to reconvene at 2 o'clock.

Marcia, do you have anything?

MRS. MOORE: No.

(Luncheon recess.)

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

CHAIRMAN DURST: We will reconvene for our afternoon session.

It turns out that we haven't been able to locate our first speaker, Steve Gendel, but we will go on then to the public comments portion.

PUBLIC COMMENTS

CHAIRMAN DURST: Since today we have only five signed-up speakers, we are going to give them 5 minutes instead of the 3 minutes that we used yesterday. Hopefully, all of our speakers are here. The first one is Alice Bast from the National Foundation for Celiac Awareness.

(No verbal response.)

CHAIRMAN DURST: She is not here; okay. Our second speaker is Elaine Monarch from Celiac Disease Foundation.

MS. MONARCH: Good afternoon. I was slightly unprepared to make a statement until I was called on earlier today, and I am more than pleased to do so.

My name is Elaine Monarch. I am the

founder and director of the Celiac Disease Foundation, a national organization for individuals with celiac disease and dermatitis herpetiformis. Our offices are in Los Angeles California.

I am pleased to thank several of my medical advisory board for making their appropriate presentations today. I want to thank this Committee for the opportunity to say a few words, and for the hard work that you are doing on behalf of all celiacs.

On behalf of the Celiac Foundation, I am an active participant in creating more awareness of this disease. As a member of the NIH Planning Committee for the 2004 Consensus Conference, I was hands on in the awareness process, and I am still involved in getting the message out to the medical community. I am also a member of the DDNC, the NDDIC, and the American Celiac Disease Alliance. It sounds like alphabet soup.

Oh, by the way, I am a celiac. I am a typical celiac. I was not diagnosed as a child. I was told that I was a banana baby, that I would

outgrow whatever stomach distress my parents said I had. I was diagnosed when I was 40. I fit right into everybody's statistics for not being diagnosed appropriately.

As validated by the 2004 NIH Celiac Disease Conference, celiac disease affects 1 percent of the total population in the United States. We have heard today that celiac disease is the only digestive disease that we know the trigger for, and we call that trigger "gluten."

It is also the only digestive disease that doesn't require pharmaceutical intervention. It can totally be controlled by the strict adherence to a gluten-free diet.

Adhering to this diet or lifestyle is not as easy at sounds as you have heard here today and yesterday. For example, there are limited choices that I will have later today as I wait an hour and a half at the airport for my plane. I could probably find drinks, possibly a banana at Starbucks, and very few other food choices.

I feel very fortunate that all I have to

eliminate from my life is gluten, yet there is no standard for how much is too much, and that is what I am hopeful will be the outcome of this meeting.

The simple casual snacking, something that most of the population take for granted, is not so for me. We need to examine everything that we ingest. There is a wheat protein in everything from Campbell's soup to licorice.

In today's busy society, fastfoods have become a way of life for most people, convenience foods. We talk to people on a daily basis in our office, they are in a quandary of what to eat. Fastfoods, sticking something simply in your mouth at a cocktail party at somebody else's home is not an option for a celiac.

There are as many stories in the celiac community as there are diagnosed celiacs and those yet to be diagnosed, and a broad range of sensitivity. We are relying on this Committee to supply our community with reliable, evidence-based guidelines so that the majority of us can live the gluten-free lifestyle to its fullest.

This past summer I am very pleased to say -- or this summer our organization sent 12 celiac children to camps across the United States where food wasn't an issue.

We put the word out through the Internet through our newsletters and our fellow celiac organizations that we had the opportunity to provide this camping experience for these children. We asked them to please supply us with essays.

Twelve essays came in. We were never going to turn anybody down. Twelve essays came in from 12 children. Their ages were between 8 and 14. Each essay focused on food.

They were afraid to eat at camp. Their parents would send for them for their other camping or overnight experiences. They were afraid that whoever was in the kitchen was going to serve them improperly.

When you take a gluten-free waffle out of a package, you have no idea if it is gluten-free or not gluten-free. If you took two, square waffles out of a package, is one gluten-free and one not?

You would have no way of knowing.

Every one of these 12 essays was based around the fact that food was an issue for these children. They didn't want to be different. They didn't want the camp to run out of food. They didn't want the camp to say, "Oh, Joey, this is your meal."

We sent these 12 children to camp. We are now just starting to get replies from the camps. The smiles on the photographs go from ear to ear. They had the best experience, because they could experience the camping experience to its fullest without the fear factor of food or being sick. They weren't different; they were just campers.

All celiacs are totally dependent on the food industry's manufacturing processes, practices, and the accuracy of labels. Diligent label reading is what we do. Yes, it does take us a little longer to go through the food store. Yes, you do have to read the label every time you buy a product.

Warnings that foods are made in facilities

that also manufacture foods that may be toxic to us, like the inclusion of wheat on a food label, is going to be extremely helpful. We see the word "wheat" and we know that we don't have to read any further.

Patient compliance will improve when there is a reliability on a food label. I think compliance is low now because people aren't sure, and they might as well cheat, because they are not too sure if what they're eating is safe or not.

Food is truly our drug of choice. The decision of this Committee will impact the quality of life of 1 percent of our total population. That is close to 2 million people.

Please decide on a standard that is healthy, and that is doable by the food industry. Thank you. Please help us to make more informed decisions so we can take care of ourselves.

Thank you.

CHAIRMAN DURST: Thank you.

Does the Committee have any questions?

Yes?

DR. KELLY: Ciaran Kelly. I do have one question. I think we are all in agreement about the importance of clear, reliable labeling of gluten-free foods. As we approach that, approaching the question of thresholds, what we are also struggling with are what the preferences of individuals with celiac disease might be.

We all know that it is going to be impossible to have zero gluten in food. The question is, How rigorous a standard of gluten-free do you think most individuals would like to see? Do they want to see a highly rigorous or a less rigorous standard?

MS. MONARCH: Well, we think that based on the information that was provided here today, 20 parts per million to 100 parts per million, I think each of us following the gluten-free diet would be safe. I think that is probably a good industry standard that the industry could comply with.

I think listening to some of the comments yesterday from the allergy people I think catering to the small fraction of people that have the most

severe sensitivities would do the entire population a disservice.

CHAIRMAN DURST: Any further questions?

(No verbal response.)

CHAIRMAN DURST: Thank you. We will go back now to our first speaker, Alice Bast, from the National Foundation for Celiac Awareness.

MS. BAST: Hello, my name is Alice Bast, and I am the executive director of the National Foundation for Celiac Awareness. I am co-chair of the Greater Philadelphia Celiac Sprue Support Group. I am also a celiac sufferer.

Thank you for the opportunity to speak with you today about the importance of clear, unambiguous labeling of food so that the estimated 3 million Americans with celiac disease can confidently choose food that is safe for us to eat.

We agree with the consensus statement published after the conference of experts convened by the National Institutes of Health, which noted that the strict definition of a gluten-free diet remains controversial due to the lack of accurate

method to detect gluten in food products and the lack of scientific evidence for what constitutes a safe amount of gluten ingestion.

These experts concluded that additional research is needed to define the minimum, safe exposure threshold of gluten in a diet relative to celiac disease.

Celiac disease is underdiagnosed, in part, because it has many forms. Patients suffering from classical celiac disease exhibit digestive tract reactions to gluten in the form of diarrhea, bloating and constipation, but many more of us have atypical or silent or latent celiac disease, and many others are genetically predisposed waiting for the disease to strike.

Unlike people suffering from food allergies, addressed elsewhere in the draft report, many celiac patients do not exhibit acute reactions to food containing gluten.

Celiac disease must be confirmed through blood antibody tests followed by an endoscopic examination of the villi of the small intestine.

The result of continual ingestion of gluten is chronic suffering in the form of: anemia, osteoporosis, diabetes, thyroid disease, infertility, stillbirths, and cancer.

With the level of complexity, it is understandable that there is not yet the consensus regarding a threshold level for gluten in the diet of a celiac sufferer. How can a no-observable or lowest-observable effect level be set when many celiac patients exhibit no obvious symptoms?

We are encouraged by the research that is underway to set a threshold, but we believe it is premature for the Working Group to recommend an approach to setting the threshold without more data.

We encourage the FDA to consider including its report to Congress on this subject a request for an appropriation to be made to the National Institute of Health to fund further research in this important area with the goal of defining an appropriate and healthful threshold level.

Gluten is not one but a family of proteins

that separately and together can trigger reactions in celiac patients. These proteins are present in wheat including durum, spelt, kamut, barley, malt and rye, and the cross-hybrids and related proteins are present in oats causing reactions in some people with celiac disease.

Flour milling and food manufacturing processes are ripe with opportunities for cross-contamination, putting celiac patients at risk of ingesting gluten from apparently safe sources.

Again, we suggest that funding be made available to develop and refine analytical methods that will enable food processors to determine the level of gluten present. We believe this is the first critical step not only in the rational food labeling program, but making food safe to eat for celiac sufferers.

Cross-contamination represents a risk that we can manage through proper equipment clean out and product isolation procedures that are routinely practiced by other industries. Providing standard

analytical methods to the food processing industry will enable manufacturers to label their food products properly, engendering the trust of celiac patients throughout America.

Thank you for the opportunity to have me speak to you today.

CHAIRMAN DURST: Thank you.

Are there any questions?

DR. MALEKI: Yes.

CHAIRMAN DURST: Okay. Soheila.

DR. MALEKI: Soheila Maleki. This could have been asked for either one of the previous speaker or you, but how does the consumer feel about the labeling of two, like a double-scale labeling, "low-gluten" versus "gluten-free"?

MS. BAST: I would have to speak on behalf of myself. I would say that we have had one incidence. There is a wafer, a communion wafer, that has been labeled as low-gluten. There are a number of people that are very hesitant in taking that, because it is low-gluten.

I think that at least they have an idea or

an understanding that there would be no gluten versus low gluten. That might be a good compromise, because they know that there are potential risks. If they are feeling that they don't want to take those risks, then they have a choice.

CHAIRMAN DURST: Ciaran, did you have a--?

DR. KELLY: (Shaking head.)

CHAIRMAN DURST: All right. Thank you very much.

MS. BAST: Thank you.

CHAIRMAN DURST: Our third speaker is Mary Schluckebeer from the Celiac Sprue Association.

MS. SCHLUCKEBEER: I want to than you all for having listened to so many different parts and pieces of this rather complex problem. You see how many questions there are? That is what we get in our office every day as we reach people who are newly diagnosed in our Celiac Sprue Association.

We get about 80 calls a day. We get about the same number of E-mails and over 2 million hits

to our Web site every month. This is one where people are looking for answers.

Like the researchers have shown you today, answers aren't real easy to come by on this. We really don't know the entire scope of the program. This is probably because after diagnosis the doctors are very pleased. They have figured out what all of these strange little symptoms finally came to, and it is diagnosed.

They are thrilled and they say, "All you have to do is just go home and just eliminate all of those amino acid sequences that you find in wheat, barley, rye, oats, and their derivatives."

And you say, "I'm not going to die." Then, you go home and you try to figure out what to do.

Well, I am one of those people who is a celiac. I was the daughter of a celiac. While I was going to the University of Nebraska as a home economist. "Oh, dad, a little bit won't hurt you." Every time he got into a little bit he suffered a lot.

At the time he was diagnosed, around 1959, the smaller tube was introduced. The doctor said, "I just read about this, and I think maybe we should check you out." It was almost a fluke that you got diagnosed around 1959, 1960.

At that time food was not labeled. Dairy products had to have their recipe on file at the state. You didn't know as a consumer exactly what was in that.

Well, at that time ice milk was almost always thickened with wheat flour, to help get that feel in your mouth. Since you take the cream out, you've got to put something in.

Oh, I never wanted to have his disease. Now, he ate bread that was this (indicating) high. I mean, that is as high as it ever got. At that time wheat starch was allowed in the diet and was in the packages that were said appropriate for people with celiac disease.

Elaine Hartsook of the Gluten Intolerance Group of North America started working with one of the companies and said, "You know, this is still

making people sick."

When they eliminated the wheat starch from these packages, my father's final symptoms of some of the rash disappeared. He assumed this was something he could eat with confidence. He figured, "It's got to be something else I'm getting into." He just couldn't figure it out. It was that little, tiny bit of wheat starch.

So I'm always a little hesitant about saying, "Oh, let's put this in" or "Let's take this out," because, again, symptoms are not specific. You can't say "I chewed this piece of gum, and I got symptoms."

You go around and you're trying to figure out, "What all did I get into in my environment in this last two or three days that may have created a symptom?"

When a person is diagnosed and the doctor says "Go home and be well and just eat," because you don't die -- researchers aren't real interested in us when there are other problems that people do die and we haven't solved and haven't gotten cures

for.

A celiac is left to have a team usually of other people who have celiac disease, or they come to support groups like ours where we have almost 10,000 members right now.

We are the largest celiac support member-based group in the Western Hemisphere, and we are very pleased. Canada has around 6,000 members in their association.

What we find is, though, that people get very comfortable after they stick around with the supports for a while and then they go off on their own, because "Oh, I'm very comfortable in my diet." I have learned how to live the lifestyle, and I really don't need the help of everyone else.

We do a survey once a year of our membership. One of the things that we did this time was ask people to self rate where they consider their sensitivity. Another question was, How risk averse are you? Because it is a very risk-averse population.

No matter what the sensitivity level a

person classified some of the cells as -- over 90 percent of the people put themselves at -- they will take no risk, no known risk, in their food choices.

That is a pretty high level of at least intent that is expressed, no matter what they say their sensitivity level is.

Again, that is why something like money for research to find this threshold -- you notice this threshold is the problem in each of these countries. There is not any real good basis for us to come up with a threshold.

That is why the physician said, "Go home and don't eat any."

When you are talking to grandma she says, "Just have a little," that's kind of where zero comes out.

It is that place-taker or a way of communicating, "I can't have some. I have to have none." I don't know, if I could have some, I have no idea how much "some" is.

It may be different when you are under

stress like in a hospital situation, at a childcare center. What kind of risk do you want to take at the training table, athletic training table, when somebody else is picking out the food for those at the table?

Again, without a threshold, it really makes it very difficult to make some of these choices because it is all subjective. Right now, it would be awfully nice to be able to say it is not subjective. We have some concrete information. This is what will work as a workable definition for the celiac patient and for the manufacturer, and it is easy to communicate all of that information to each other.

Thank you.

CHAIRMAN DURST: Thank you.

Any questions, Committee?

(No verbal response.)

CHAIRMAN DURST: I think there are not. Thank you.

(Sotto voce discussion.)

CHAIRMAN DURST: Our next speaker, also

from the Celiac Sprue Association, is Tom P. Sullivan.

MR. SULLIVAN: Good afternoon and thank you. My name is Tom Sullivan. I happen to be the president this year for the Celiac Sprue Association. I myself am not a celiac. However, I have very, very good association, and that may be one of the reasons the patients decided that I should be their president this year.

I have a wife who is a celiac; I have a son who is a celiac; and I have a great niece who is a celiac. The horror stories that lead to the 11 years' average time for diagnosis I can perfectly well relate to and admit to. Because I sat in a gastroenterologist's office and shook my head most emphatically no four times to force that man to take a biopsy on my wife.

The man never spoke to me again, never looked in my direction after coming out of the biopsy room. It was flat out knowledgeable on his face what she had. It took that kind of forcing effort.

Education is still necessary. It is a major factor. It is one of the reasons CSA exists. When a patient is diagnosed, they are informed basically "Go and sin no more, my child. Change from a wheat-based lifestyle to a rice-based lifestyle. Goodbye" (waving).

What the heck does that mean? I haven't a clue. It turns out the only ones who have a clue, who know what to buy, where to buy it, who sells what, how to use it, what do I do in my kitchen, how do I travel, who do I see for this or that problem, what does this symptom mean are other celiac patients.

That is why CSA came to be, that is why its mission is to be celiacs helping celiacs, and that is why its function is to be the voice of the patient. The patients are very, very good. We go out with surveys each year, and they tell us what do we need, what don't we need.

With reference to this afternoon's proceedings or this week's proceedings rather with this draft, the draft is a very good working draft.

It agrees with the patients, and that is, the risk-assessment method is the method of desire.

In fact, the patients themselves have moved to a risk-assessment process. It has been done intuitively, it has been done with cross-communication among all of them, and it has produced the capabilities that CSA currently has to speak for the patient.

What the patient does is very simple. They say, "I have to eliminate wheat, barley, rye and oats." Let's not talk gluten. Let's get away from the. Source ingredients of wheat, barley, rye and oats; okay? So my target is zero. Now we all know, scientifically, zero is unmeasurable.

That isn't the situation. I have a problem. I want none of it. How do I do it? Now we get practical. Now we start asking manufacturers, "What levels are you at? What do you do? Can we trust you? Are you consistent?"

We put together lists of products. This year's product listing is approximately 70 pages listing products that the manufacturers will stand

behind, because they have told us that they do not use wheat, barley, rye or oats in their product, in their packaging, or in their processing. It is a great source to help people get started.

In fact, one of the fun things I have when I get an E-mail or a telephone call -- and it comes from all over the world by the way, both into the office and personally -- my immediate reply is "Relax, take a deep breath, and let it out very slowly. There is life after diagnosis." Then, we teach them how to do it.

From a practical standpoint, the patients evaluate the products that are out there. They evaluate them against their target of zero, and they handle them as a result of their reactions to the ingestion of that product.

If they have a problem, they go look in the book and find another similar product, a different brand name, or they go to another label of the same product in the store.

However, they have a method and a technique that they have instinctively gone to, to

say, "How do I protect me? I have a health problem. How do I protect me."

A very interesting result of this is that when the patient starts on the gluten-free diet they very quickly become better. This is why you end up with a very wide range of variability in your responses and in the reactions because most of them, by and large, don't ever want to go back there again. They didn't like it; they don't like it; and they don't want it repeated.

One of the things that has helped is the labeling and the information available out of the manufacturers, the fact that they will respond, the fact that the patient community is getting much, much better on their knowledge of the questions to ask and who to go to.

For example, not too long ago it was very common to just pick up the phone and call the manufacturer and say, "Do you have gluten in your product?"

"Yes."

Okay, forget that product. Now, the

question is because rice gluten and corn gluten are no problems, most of the patients will now ask, "What is the source of that ingredient?"

"Oh, it's corn."

"Thank you." Problem solved. They have set the risk level at zero. They have evaluated the products that are out there, and they have communicated that among themselves. That is celiacs helping celiacs. That is what keeps them safe. That is the way they have done it.

I am very, very happy to see that that is exactly the way you have chosen as the recommended technique for doing it. I think in the long run it is the only one that is going to do it, what is the minimum level. Beyond that, then, I've got problems I can go looking at. Right now, we have nothing. I think it is a very good start. Thank you kindly.

CHAIRMAN DURST: Thank you.

Do we have any questions?

CHAIRMAN DURST: Do we have any questions?

Soheila.

DR. MALEKI: Sure. I guess I'll pose the same question as far as previously, How do you feel about two-scale labeling such as low gluten versus gluten free?

Sorry, Soheila Maleki.

MR. SULLIVAN: That is a question we have not yet asked our members, so I can't answer for the membership. That is a question we will ask on this year's survey, however, and we will have the answer for you probably sometime just after the first of the year.

Personally and based upon the input I've had from the other celiacs over the years, if a definition is precise and they can depend upon it, then I don't think they will have any problems.

Quite frankly, a celiac patient is one of the smartest people you're ever going to meet. It is their health, their body, and they and they alone are completely responsible for it.

By the way, at the end of September of this year and the first of October in Tyson's Corner, CSA is having our National Annual Education

Conference. You are all invited to come and find out what the patients think and why they think it.

They will ask you some of the toughest questions. It is a shame I didn't have Dr. Murray say that this morning, because he has admitted they ask nasty questions.

(General laughter.)

MR. SULLIVAN: They want to know because it is my (pointing) body, and it is my responsibility solely and completely. You tell me, and I'll make the decision for me. That is where it is coming from. It is more information. More information is always to our benefit as a patient.

CHAIRMAN DURST: Ciaran, did you have a question?

DR. KELLY: That addressed it.

CHAIRMAN DURST: Okay.

Anything else from anyone?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

MR. SULLIVAN: Thank you.

CHAIRMAN DURST: Our final public comment

speaker is Steve Taylor from the University of Nebraska.

MR. TAYLOR: Good afternoon. My name is Steve Taylor, and I am a professor and co-director of the Food Allergy Research and Resource Program at the University of Nebraska.

In addition to what you all heard from me yesterday, our group provides analytical services to the food industry including gluten testing services, so I thought perhaps I could get up here and say a bit about testing methods.

I should also say that this is a fee-for-service activity that we provide to the industry, but we also provide services on a lesser cost basis to the Celiac Sprue Association and to the Food Allergy and Anaphylaxis Network.

I want to make several points. One is about testing methods and frequency. Our laboratory uses the R5 monocle antibody test that you have heard about this morning. That test is commercially available from a company called R-Biopharm in Germany as an ELISA kit. There are

other equivalent test methods that are on the market as well.

This test detects prolamins, the prolamins gliadin from wheat, secalin from rye, and hordein from barley. It does not detect oats but will detect the presence of wheat, rye and barley proteins in oats, which is perhaps somewhat of a significant concern to celiac sufferers. Our advice is that they continue to avoid oats in North America because of the chance that oats could be contaminated with wheat, rye or barley.

The test detects the prolamin proteins more reliably than it detects the glutelin proteins, the higher-molecular weight ones, but we can very easily detect the gluten levels in wheat starch and other ingredients that you have discussed today.

I think this test is very reliable for the food industry to use to determine whether the products are gluten free. I can say that the food industry in North America has been using this and similar tests for a number of years now to help

assure that products that are labeled gluten-free indeed fit that definition.

I can say that it is my experience that the industry is doing a much finer job in that regard than perhaps they were 6 or 7 or 10 years ago. That is partly because the Government of Canada established this regulatory framework that you have heard about this morning.

In the countries where the legislation has said "gluten-free" is "zero," it can't get to zero, so operationally you still have to have some definition of it. The Canadian Food Inspection Agency uses less than 20 parts per million as their operational definition of gluten-free.

When they established this regulation in 1996, they began to be very vigilant in the analysis of U.S.-made, gluten-free products crossing the border into Canada to be sure that those products met the definition. Well, most of them did not.

They met the previous definition that you've heard about this morning, the Codex

Alimentarius Commission's definition of less than 200 parts per million, but did not meet the definition of less than 20.

I can tell you that since 1996 till today almost all of those companies have succeeded in protecting their Canadian market by now adhering to the less than 20-part-per-million standard.

If you establish a standard of zero, many of these companies will not be able to produce gluten-free products because zero is unattainable. We have heard that from some of your speakers this morning.

I also want to say a few words about grain-add mixtures, because the adventitious presence of one grain in another grain is allowed by something called "USDA grain standards." Wheat can be in oats, soybeans can be in corn, soybeans can be in wheat. That is allowed by USDA grain standards, which are recognized around the world.

Raw agriculture commodities are another exemption that is in the FALCPA legislation. I think this establishes another potential

consideration for the panel in terms of a statutorily derived threshold.

Once you convert these raw agricultural commodities that are exempt into milled wheat flour, milled oat flour and milled cornmeal, then they are not exempt anymore.

Yes, if you establish a threshold at zero, then this contamination occurs on the farm, and there is no way to completely prevent it. However, it is quite possible to have safe and effective gluten-free products meeting the strictest definitions in the world, those of Italy and Canada, with less than 20 parts per million gluten. I was convinced by the data I saw this morning that seems to protect the vast majority of celiac suffers.

Thank you. Dick Durst. I have question on what the Canadians use as far as their method of detection? What is the limit of quantitation on their immunoassay?

MR. TAYLOR: I think they use the same test that our laboratory uses, which is the

R-Biopharm Test. R-Biopharm sells several different tests. I wish Dr. Hefle were still here. I think the limit of sensitivity of the tests that we are currently using is in the neighborhood of 5 parts per million slightly lower than that.

CHAIRMAN DURST: Okay. The limit of quantitation is right near the limit that is set, this 20 parts per million?

MR. TAYLOR: Well, it is severalfold below that. I mean, it is 5 parts per million and the limit is 20.

CHAIRMAN DURST: Yes. Well, the limit of quantitation, I would think, is what you would need to use in order to really verify the amount of gluten or whatever or prolamin that is in the product. I'm not sure the limit of detection is the kind of best characterization.

MR. TAYLOR: Yes. The limit of quantitation with that test is in the neighborhood of five parts per million. I don't know what the lowest limit of sensitivity is. We know that we can reliably test 5 parts per million with that

test. I know Dr. Hefle knows the answer to that question, I just don't.

CHAIRMAN DURST: Marc had his hand up?

DR. SILVERSTEIN: Marc Silverstein. Do manufacturers continually test during production, or is it just in developing a new product for the market?

MR. TAYLOR: It has been our experience that many of the producers of products that are labeled gluten-free test rather frequently. There are several very noteworthy companies that make gluten-free products that are rather popular among celiac sufferers, and these companies test very frequently.

One that I can cite as an example would be Arrowhead Mills, which was one of our more frequent clients for a number of years. They were doing so many analysis that they built their own laboratory at the plant in Texas, and they do the ELISA testing on a regular basis in their own facility.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Yes. I just want to say that

you brought up a really good point about the farmers that grow in and have rotation crops. That essentially brings up a good point. I don't think you could ever reach zero, even just because of that, because of the same trucks they use, the same dirt it is grown in, and so forth.

MR. TAYLOR: Yes. I mean, it is the same farms, the same farmers, the same harvesting equipment, the same on-farm transportation, the same elevators, the same off-farm transportation. The system, the commercial system, for handling grains in the United States and around the world doesn't offer you the opportunity to get to zero.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Yes. Is it possible, though, to drop somewhere between twenty versus zero? Is that realistic at all? Or, do you really think 20 is as far as you could go? Could you go to 10?

MR. TAYLOR: Well, you can do anything you want with the analytical testing capabilities. I think I would defer to the clinical experts, that

we have heard from already here, about what the threshold level for celiac sufferers ought to be and the way that ought to be established.

We don't do any clinical research on celiac disease. We avidly read their papers, but we are just analysts with respect to celiac disease, and we do not pretend to be clinical experts on this difficult subject.

I mean, in terms of being able to make products that would pass that standard, 10 versus 20, would that make a big difference in terms of making products?

MR. TAYLOR: Well, to me does 10 versus 20 make a difference? It depends upon whether it makes a difference to the celiac sufferers in terms of their health status.

The industry struggled when we went from 200 to 20. Many of them already could probably come close to meeting 10, if they don't already do it. Some of them might struggle to get there. Consistently? Consistency is another key point.

CHAIRMAN DURST: Jeff.

DR. BARACH: Yes. Jeff Barach. Could you speak to the validation of the test that you described, the monoclonal antibody test? Do you know if it is validated?

MR. TAYLOR: Well, I don't know if it has been "validated" by the procedures that FDA prefers to use when it uses that term, but it has been validated by the company that made the kit. The Prolamin Working Group has done some interlaboratory testing of that kit as well. I am not so sure that there have been comparisons between that test and tests by competing companies that are largely similar, so there may be some analytical work to do. I am not so familiar with the Prolamin Working Group. Dr. Hefle follows that group, but I don't.

CHAIRMAN DURST: Margaret.

DR. BRILEY: Margaret Briley. Could you give us any kind of estimate of the cost factor for industry in terms of how often they use this test and what it would add to the cost of the product?

Once you start testing it, I would think

you would test everything that came through, whether it was for celiac or not. Am I wrong? I mean, if you're going to run a test, wouldn't you just run it? You're putting it out as an industry. You wouldn't do a separate run just for celiacs?

MR. TAYLOR: Well, that is a very complicated question as to how frequently you test, how you devise a credible sample plan, and whether the results of your test are reliable in terms of all of the product manufacturers. Obviously, you can't do a test on ever package of product, because then you wouldn't have anything left to sell.

(General laughter.)

DR. BRILEY: No.

MR. TAYLOR: The tests are not very expensive in some terms. We charge $50 to $75 for the test per sample. I mean, that is some cost and companies are going to question whether they want to do 100 tests, 1,000 tests or 10,000 tests, because it I going to be a cost factor.

DR. BRILEY: Well, I guess I was thinking that you would probably test a run. You wouldn't

test every package that came out.

MR. TAYLOR: Yes. You've got to design your testing system very strategically depending upon where you think your sources of contamination are.

Companies typically test the source materials that are coming into manufacturing. They test the first product manufactured after changeover, if they have shared equipment.

However, you've got to pay attention to things like whether you think there are hangup points in your manufacturing equipment. That varies from facility to facility and line to line.

DR. BRILEY: From company to company.

MR. TAYLOR: I wouldn't give the same advice to every company.

DR. BRILEY: Okay. Thank you.

CHAIRMAN DURST: Ciaran.

DR. KELLY: Dr. Taylor, thank you. Ciaran here. I'm going to keep you on the podium for another moment or two.

We heard about the line spots in the

currently available test, the inability using the widely used test to detect gluten in oats. Are there to your knowledge intrinsic, technical challenges there, or is it simply that nobody has bothered to try?

MR. TAYLOR: I don't think anyone has tried to develop a test for oats. I am convinced you could develop an ELISA test for any protein-containing food known to man. Yes, you could develop a specific oat test.

There is this debate about whether oats are safe or unsafe, the companies that were developing these tests for gluten-free products targeted these peptide sequences in wheat, rye and barley. You could argue that is what they should have done. I would advise them to do the same thing.

CHAIRMAN DURST: Anything further?

(No verbal response.)

CHAIRMAN DURST: Thank you.

Okay. Now we will jump back in time to hearing Steve Gendel, who is now with us, to speak

on the overview of approaches to establishing thresholds for gluten.

OVERVIEW OF APPROACHES TO ESTABLISHING THRESHOLDS: GLUTEN

MR. GENDEL: I guess I can say that one way of keeping people from going into an after-lunch slump is to mess with the agenda. You have to pay attention to know where we are. I'll take credit for that.

(General laughter.)

(Slide.)

MR. GENDEL: What I'm going to do today is going to be an abbreviated form of my shortened talk from yesterday, again, just to serve as a refresher for what is in the "Draft Report"; to set the stage for your discussion; and, again, to remind you that the purpose of the report is to identify approaches that can be used to establish thresholds, not to decide on which approach to use and not to discuss specific threshold values. We are interested in potential approaches, the advantages, disadvantages and data needs of each.

(Slide.)

DR. GENDEL: The organization of the report hasn't changed since yesterday. There is a section where we review celiac disease and one which we talk about the approaches we have identified for setting thresholds for celiac or for gluten.

(Slide.)

DR. GENDEL: In the section on celiac disease, we reviewed the mechanism of pathogenesis, information on prevalence, foods of concern, we looked at the clinical challenge studies that were available, and looked at issues related to measuring gluten in food -- all of the things that we have heard about this morning.

(Slide.)

DR. GENDEL: As with the allergens, we identified four potential approaches, and really in this case three: the analytical methods-based approach, the safety assessment-based approach, and a quantitative risk-assessment-based approach.

I mentioned the statutorily derived one here, for the sake of consistency with what we talked about yesterday, where we felt that there was no language in FALCPA comparable to that for allergens that could be applied in the case of gluten.

(Slides.)

DR. GENDEL: I am not going to go through these approaches again. I think you are familiar with them. The analytical-methods-based approach, which is based on the sensitivity and detection methods available; the safety-assessment-based approach relies on LOAELS and NOAELS from clinical data and appropriate uncertainty factors based on the gaps in those data; and the risk-assessment-based approach; and the quantitative approach, which takes all of the dose response information available into account.

(Slide.)

DR. GENDEL: The findings of the Working Group, there were again five, the first one again to reiterate the fact that whatever approach -- if

a decision to set thresholds is made, whatever approach is chosen at this time, that these decisions should be reevaluated frequently as new data became available.

We heard a lot of discussion this morning about clinical studies here also that are in progress, and new data will become available. We recognize the fact that any decisions made in the short term should be reevaluated periodically.

The Working Group found that the analytical methods-based approach could be used for gluten also. However, as we talked about yesterday, if it is used, we feel that it should be replaced by a risk- or public-health-based approach as soon as that is feasible.

The safety-assessment-based approach, the Working Group found that approach could be viable also based on data from the literature and appropriate safety factors, taking into account the nature of the clinical studies available to use.

The risk-assessment-based approach we felt was not feasible at this time due to the lack of

data to quantitate risk in a dose-response type manner.

Finally, as I mentioned, the statutorily derived approach is not viable due to the lack of appropriate statutory language.

That is really all I have to say about the report. Are there are any questions about the report itself?

QUESTION AND ANSWER SESSION

CHAIRMAN DURST: Thank you, Steve.

Do we have any questions?

Ciaran.

DR. KELLY: Yes -- Ciaran Kelly -- just a technical question. When we are talking about the safety-assessment approach, does that include population observations in addition to prospective studies? We heard this morning about a prospective study, retrospective studies, and clinical experience with a population that have been using particular standards for many years. Is that information incorporated within a safety-assessment approach?

DR. GENDEL: I would say that the safety-assessment approach would be one where any data that can be used to establish a LOAEL or a NOAEL is used. Then, depending upon where those numbers come from with that number, then you would apply appropriate uncertainty factors, and the nature of the data which goes into establishing those numbers would then be taken into account as uncertainty factors would apply.

DR. KELLY: Would it be true to say, then, that if similar numbers were arrived at from different sources in the data, if independent studies using different methodologies all arrived at a similar number, that would reduce the uncertainty factor?

DR. GENDEL: I would say that is probably fair. Anytime you can replicate data, the degree of uncertainty associated with it is less.

CHAIRMAN DURST: Any other questions for Steve.

(No verbal response.)

CHAIRMAN DURST: All right. Thanks,

Steve.

DR. GENDEL: You're welcome.

CHAIRMAN DURST: We are now scheduled for a break. We are about 15 minutes ahead of schedule, so we will take our 15-minute break and reconvene at 3:15.

Thank you.

(Thereupon, from 2:55 p.m. to 3:15 p.m., there was a pause in the proceedings.)

COMMITTEE DISCUSSION

CHAIRMAN DURST: Would everyone take their seats please, and we can continue the afternoon session.

All right. At this point I guess Steve just before gave a nice review of the charge and the questions that we are supposed to address. What I would propose is that we initially begin with just open discussions of the general points on celiac disease; then address some of the specific questions; and then, finally, if there is time at the end of the day, also open discussion again on the allergens and perhaps any cross-reference to

the celiac disease. There are certainly similar questions in both of those cases.

I would like to mention, just to expedite tomorrow's discussions, I have asked three members, Marc and Suzanne to deal with the allergens and Ciaran to deal with the gluten, try to come up with a summary or a consensus of what they felt our discussions have been leading to in terms of how we want to address these approaches for setting the thresholds.

I think that would help us in the morning to focus in on those particular aspects and, again, have the discussion bring in any new points or additional points that members may want to add to those summaries. I think that is all I want to say on this point. Let's open the discussion on the gluten and celiac disease.

Does anyone want to start with any general comments on that?

Soheila.

DR. MALEKI: Soheila Maleki. I actually have questions. Is that appropriate at the time,

at this time, to ask the panel questions?

CHAIRMAN DURST: Yes.

DR. MALEKI: Well, I have some questions for Dr. Fasano. Well, I've got multiple questions, but I will try to go through them where you can answer them. What is it the specificity of the activated CD3 T-cells? Do you know if they are gamma/delta, alpha/beta, CD8, CD4?

What is particularly their specificity as far as are they transglutaminase-specific or the PEQ-specific? Anyway, do you know of any studies that have looked at gluten-specific T-cells that actually are reacting to oats or one of the other products? How about the antibody cross-reactivities of gluten versus barley, wheat, and then oats? I think that's it.

(General laughter.)

DR. FASANO: Let me tell you the facts the way we know right now. The activation of the intraepithelial lymphocytes, particularly through CD3 and gamma/delta, are considered highly specific for celiac disease.

As a matter of fact, in the early Marsh classification, Marsh I, we don't have any damage whatsoever but you have all the infiltration, intraepithelial infiltration, into the lymphocytes.

If you want to know that is malignancy of the disease, you do the specific CD3 staining. If it is positive, then you can say, "Okay, this is Stage 1 of a Marsh grade for celiac disease."

Yes, as far as we know, there are gluten-specific T-cells epitopes. You can isolate T-cells for gluten or a fraction of gluten in terms of a reaction activation of T-cell and K-cells and so on and so forth. Absolutely, that is the way to do that.

Of course, the specificity of transglutaminase is an issue that is out there. The only thing that I can tell you, at least based on serological data, i.e., how specific is tissue transglutaminase or inflammation-related celiac disease, I would say that it is fairly specific, with a few exceptions.

If it is true the current theory that the

reaction to transglutaminase is due to an initial insult of the cells, it leaks transglutaminase, and therefore becomes not naive anymore to the immune system, leading to the immune response.

If this starts at the intestine level, there is some specificity with celiac disease as compared, for example, to Crohn's disease in which we don't see that. However, we see patients with Type I diabetes, for example, and not co-morbidity with celiac disease in which the insult translates with increased antitissue transglutaminase antibodies.

In terms of cross activity among grains, I will not give rights to the arguments. I believe that Don will be much better than I am to give you that kind of response. I can give you an unprofessional, amateur response. The general wisdom is, yes, there is cross-reaction.

DR. MALEKI: At T-cell level also?

DR. FASANO: Say that again?

DR. MALEKI: At the T-cell level? Of course, yes.

DR. FASANO: Yes.

DR. KASARDA: At the T-cell level? Is that what you said?

DR. MALEKI: Both actually, antibody and T-cell.

DR. KASARDA: That is difficult to answer. The problem is that almost all of the studies focus on wheat, and very little has been done with rye and barley.

As far as immunological epitopes are concerned and cross-reactivity with IgG and IgE and probably IgA, yes, there is a lot of cross-reactivity because there is sufficient homologies. However, when it comes to the T-cell and the T-cell receptors, that is a whole other ball game. I can't answer that. Maybe Pekka Collin can.

DR. MALEKI: Thank you.

DR. COLLIN: I would say about gamma/delta T-cells that they are thought to be very specific for celiac disease, but we are a little bit disappointed. I think specificity and sensitivity

for increased density is about 90 percent. The strongest evidence against that they would be specific is that in many cases those with elevated gamma/delta T-cells they do not share their DQ2 or DQ8, so they probably are not celiacs.

DR. FASANO: That is gamma/delta. The CD3, that is the one that I was talking about, that seems to be much more specific.

DR. MALEKI: Thank you.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: I have a totally different question.

CHAIRMAN DURST: Okay.

DR. BRITTAIN: Yes, it is about the Italian study again. As a statistician, it is my job to be skeptical. I just wanted to ask, and I know that you have demonstrated there was a difference between the placebo group and the 50-milligram group. You didn't see a statistically significant difference between the zero and ten. In fact, the means were very, very similar.

Normally, when you want to show that two

groups are equivalent or similar, you would construct a confidence interval to define that difference and estimate that difference. Is that something that has been done?

DR. FASANO: Yes. The analysis for the villus/crypt ratio was done on a confidence interval level and there was no overlapping. However, I have to be super-duper skeptical and say that a morphometric measurement is not as accurate as any other biological readout that you can consider.

In other words, it is operated dependently of course. That is how you make the measurement. It is not a machine, so there is some degree of possible error in there that you have to consider.

Nevertheless, if you did this in the blind fashion, as we did, if you have two operators and there is a 100 percent concordance, as happened to us, the level of confidence that that was right increases.

A more objective measurement, i.e., the intraepithelial lymphocytes for which you say, "I

want to know how many there are per hundred entrocytes, per hundred T-cells."

Why are we saying that 50 milligrams may create a problem is because, again, we want to be extremely conservative -- if we say, "Well, actually this data is suggested but not conclusive for damage" -- the answer is yes. We don't want any question marks. It could be suggested, but that is not the way that we want to go.

Conversely, with 10 milligrams, no matter how you go, if you look at the intraepithelial lymphocytes, if you look at the gamma/delta, if you look at the alpha/beta that we did -- I didn't have the time to show all the data -- in other words, if you look at all of the parameters that you can conceptualize to look at for possible histological, serological, clinical evidence of a reaction, we consistently in all of these patients found zero reaction.

Consequently, our level of confidence is associated also to the many years of implementation of that threshold; there have been hundreds. That

makes us to say with some level of confidence that we feel comfortable with 10 milligrams while with 50 we do not.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Just one quick follow up on that. That is part of the reason I was asking this question is you would have to have biopsies to get T-cells. Is that like some type of valid immunological method to try to test for dosage, and so forth, although it is in vitro? Could that be some method, too, you would look at exposure, and so forth?

DR. FASANO: I hate to be the one to answer all the questions here. Depending on the scientist, you will find different answers. There are people that strongly believe that if you take blood and you isolate its lymphocytes and you do this exercise in vitro, it reflects exactly what is happening intestinally also.

For example, the group from Australia is trying to develop a vaccine for celiac disease. The types of screening that they are using to

establish the many peptides can be toxic or immunogenic, which one they have to look at, and you target it for a vaccine.

They use an immunoblock reaction in which they take blood from patients with celiac disease to see with these peptides which one will react and which one will not by the reaction of interferon-gamma.

The skeptics of the group will say, "Well, not necessarily does this reflect what happens at the mucosal level." Technically, that is not necessarily the same lymphocytes.

You can make an argument that you can test negative in vitro, because you don't have the right cells to migrate from the gut into the systemic circulation. I don't think that there is a final argument either way to sustain that you can do this in vitro versus the biopsy.

CHAIRMAN DURST: Ciaran.

DR. KELLY: Ciaran Kelly. I've got a question for Drs. Collin and Fasano. It relates to a safety-assessment-based approach again relating

to data, historical data.

Both of you mentioned, but I wonder if you can expand a little, upon studies that have looked at the outcomes of individuals on gluten-free diets set at certain levels as regards morbidity and mortality outcomes. You both mentioned it. I wonder if you could tell us a little more maybe about the methodologies and results of these studies?

MRS. MOORE: Excuse me, I'm sorry. When you reply, say your name.

DR. COLLIN: Pekka Collin. If you look at the mortality figures and risk of malignancy, I think the most quoted paper is from Dr. Holmes where he showed that if the patient stays on a gluten-free diet for five or six years the risk virtually disappears.

At that time, I think it was from 1984, I think that diet was not so strict as today. I suppose that at that time also people in the United Kingdom they used the wheat-starch products. The difference was between those who are on

gluten-free diet and between those who are on a normal diet, which is very seldom today that people are on a totally normal diet.

Then, the group from Italy, Corrao, the excess mortality, it was all due to those patients who had dietary lapses or who did not maintain the gluten-free diet.

In our own studies, the first had 300 patients. We did not find any extra malignancy and mortality in patients who were not on a gluten-free diet. Now, later we have our odds ratio for lymphoma, which is about four. It is almost the same as that Peter Green had in New York and what was in Corrao's paper and in the latest papers also from Sweden.

However, each case except one has been not on a strict gluten-free diet, and the majority have occurred immediately, as I told you, after the diagnosis of celiac disease. Probably, they had celiac disease and lymphoma simultaneously. Only one patient with celiac disease, presumably, on a gluten-free diet developed lymphoma.

I think that all of the evidence shows that if we try to avoid lymphoma, we should detect the cases early enough, then put them on a gluten-free diet, take care that they are on a gluten-free diet, there is some circumstantial evidence that those patients who remain undiagnosed and who are asymptomatic the risk of lymphoma there in them is very low.

In the United States, I don't know, maybe you have 200 million people or even more, and you should have 2 million with celiac disease, the majority is undiagnosed.

Still, I think that small-bowel lymphoma, especially small intestinal cancer, they are very rare even here. That would be a serious risk factor, I think we should see a lot of lymphomas here.

Our mortality risk, our odds ratio is now 1.2, so it is very little excess mortality, and it depends on the appearance of lymphoma at the same time as the celiac in the patient.

DR. FASANO: I believe that what you are

looking for is if there are any systemic studies that would compare 20 versus 200 versus 400, and of course there is none. However, there are studies that Pekka already outlined between people complying and people admitting to being less than compliance. The lymphoma probably is the least proper variable outcome to look at, because it is very rare to start with.

I am not a biostatistician, but I am assuming that if you are dealing with a condition that is one in a million, that will go to 1 in 890,000, it is hard to make the difference.

However, if you see co-morbidities, autoimmune diseases like diabetes or Hashimoto, in which you reach as high as 17 or 18 percent, then you start to really look at the differences in which you have an outcome such as osteoporosis, the same story, short stature, and so on and so forth.

DR. KELLY: Ciaran Kelly. Yes, I know there are no systematic studies. I was more wanting you to elaborate on the experience, the clinical experience, for many years at different

levels of definition of a gluten-free diet.

It seems as though there is a lot of experience with 200 parts per million, 100 parts per million, and 20 parts per million. I am trying to get a sense for whether there have been any studies to determine differences in outcomes with those different levels.

DR. FASANO: Alessio Fasano here. Again, in Italy the switch from the 200 parts per million to 20 parts per million occurred, again, six or seven years ago. There are no published studies to show if this which translated into decreased co-morbidity of that outcome.

The general wisdom for what is in there, in terms of the co-morbidity reports within the Celiac Society in Italy, seems to suggest that indeed there has been a decrease of some of the co-morbidities -- particularly, anemia, osteoporosis, short stature, and miscarriages, the fourth -- following the switch. However, these are very anecdotical, and I don't think there is such a strong scientific outcome to make that statement as

a scientifically acceptable one.

DR. COLLIN: We have experience in Finland that the important deviation is not between 200 milligrams and 50 milligrams. I think I do not have a very strong scientific evidence but only experience in what you were asking. I think that the risk of lymphoma in those patients is very, very low.

The problem is that we do not know what our wheat starch was 15 years ago when everyone also was using them, but it is logical to assume that it may have contained even more wheat or gluten as today. Even at that time, we did not have any increased risk of malignancies. It has been similar all the time when we have had this follow up since 1970 or 1975.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. One of the questions that comes up in study conditions such as allergic diseases and celiac disease is the spectrum of disease and selection or selection bias in patients who enter studies and about whom we

make inferences to the larger population.

As I'm understanding the available data, it seems that clearly there would be a large number of individuals who would have serologic evidence and genetic susceptibility.

It seems there would be a large number of individuals who probably have the disease, who have manifestations that would be detectible were they evaluated, but because they have very mild symptoms don't come to attention.

What I'm asking is, then, would it be your sense that the spectrum of patients who come to clinical attention who have symptoms, who go to medical centers, who ultimately get diagnosed, even if it is 11 years on average later, that spectrum of patients would be more severe?

Would they be more severe than the general spectrum of patients who might be in the population with a genetic predisposition, perhaps, with some inflammatory changes in their bowels, yet are not under medical care, so that the "selection bias," if you will, is to exclude the relatively mild

disease and the ones you see would be the more severe disease in the general population? I guess it is a question to Dr. Murray, who is not here. Dr. Kelly might step in and comment.

Dr. Collin.

DR. COLLIN: Of course, if you detect more and more patients with celiac disease, then the figures become less biased. We have a lot of people who are asymptomatic, patients with celiac disease. The question is very complex.

On one end, on one side, we have a patient who has very mild, mild inflammation and very mild villous shortening in the mucosa, and they may have some symptoms such as iron-deficiency anemia. On the other end, we have patients who have totally flat mucosa, and they are totally asymptomatic.

We have learned a lot of data from family studies where we are actively screening all of the celiac disease patients. We have seen truly asymptomatic patients who will not be detected without the serology screening. Still, we do not want to extend the screening program to the whole

population.

I think our policy is that we apply screening in risk groups and if they have even minor symptoms and then we can achieve almost 1 percent of celiac disease, clinically diagnosed. I'm not sure whether I answered your question. I couldn't hear it very well.

DR. SILVERSTEIN: May I follow up? There is a paper, also from Finland, the prevalence of celiac disease in children in the New England Journal paper a couple of years ago. Again, that was serologic, serology was available, so you had population-based samples.

Those who had abnormal serology, when they were followed up, and then you found some spectrum of undiagnosed disease in those children. It would seem to me the children detected through that type of mechanism, would have generally milder disease than those who would have come forward because of the clinical presentations.

DR. COLLIN: Yes. In that paper, I think the prevalence was not 1 percent, more than

1 percent of people, children in Oulu, Finland. You are right, I think many of them who were not detected earlier for celiac disease, who were detected by this serologic screening, they were asymptomatic.

We have also carried out some quality of life studies from those patients who have been screened for celiac disease not due to symptoms but because they belong to the risk groups.

We have seen that their quality of like with these measurements that we have used are very similar to that of the population in general, and it is better than those who are symptomatic patients.

With a gluten-free diet, it still increases, and it becomes after one year even better than in the population. We call it maybe a honeymoon period. We have no long-term data on that, but that is very interesting that many people really are asymptomatic.

DR. FASANO: Alessio Fasano. Marc, you are absolutely right. The people that come to our

clinic with symptoms definitely are the biased part of the population with celiac disease because they are the ones that have symptoms that seek attention. It is undisputable that compared to the overall picture of celiac disease, the one that we see on the clinical grounds are biased in that direction. No question about it.

However, for example, it is policy for us right now that every single time you make the diagnosis of an individual the entire household is screened.

Epidemiology studies out there suggest that up to 10 percent of first-degree relatives they have the disease, irrespective of if they have symptoms or not. Sometimes when we diagnose these people that apparently are completely clinically silent, you do a truly, you know, well-done workup, they have osteoporosis or osteopenia.

How would you consider the otherwise completely silent? If you make the diagnosis on time, and according to the current literature "on time" meaning two to five, you can fix and correct

the problem. If you are too late, you can't do anything about that in these people.

I would consider that a great, great danger, even if clinically they are absolutely silent because these are people at risk for fractures in their thirties. We have seen these cases.

DR. SILVERSTEIN: If I could follow up -- in terms of the spectrum of disease, unlike the situation where you have a patient with perhaps a food allergy, who we heard about yesterday, whose physician or family member or even the patient may decide the risk of the food challenge test would be too great and they would be excluded, in your experience in caring for patients with celiac disease, is there a similar phenomenon where the patient who were more severe would be less likely to undergo evaluation biopsy or participation in studies?

DR. FASANO: In terms of a challenge, in other words, I'll give you a practical scenario. An individual comes to our clinic because they have

symptoms for many years. They have never been diagnosed, but they spoke with a friend or a colleague or a family member that raised the issue of the possibility of celiac disease.

They go on a gluten-free diet without being diagnosed, and they are feeling better. They come to your clinic, and they want to know if this could be a definite diagnosis or not. You say, "The only way to do this is you have to do a challenge."

If this individual had a really hard time in his or her life -- in other words, the symptoms are severe -- the likelihood that this individual will accept the challenge is much lower than the person that had the stomachache or the bloating here and there with vague symptoms that now are gone away.

However, they want to know for sure, because now they realize that a gluten-free diet for life is not a joke, that this is indeed the kind of direction to go. That individual is more likely amenable to a challenge.

However, an individual who has been absolutely sick with tremendous symptoms that affect their lifestyle, that individual will be very, very unlikely to be open for a challenge. That is my personal experience.

DR. KELLY: Ciaran Kelly. Just to expand upon the question, that is certainly the case. That is certainly my experience. However, we are talking about clinical gluten challenges. Do you think it is the same for a prospective study where one would be performing a low-dose, a minimal dose, gluten challenge? Do you think that highly sensitive individuals would also be less likely to participate?

DR. FASANO: I think that there is a serious possibility. In other words, when you do a prospective study like the one that was done in Italy and say, "Look, there is a chance that we're going to give you a placebo, i.e., water and you're going to be all right, or you could get some amount of gluten that we don't know if it's going to harm you or not," if this individual has a really hard

time, that individual will probably be less likely inclined to participate.

Saying that, though, of the people that have participated in this study, there was the entire variation of the spectrum, if you wish, of a gravity of symptoms. I can't tell you if there were people that claimed to be hypersensitive to gluten, those that will react like two hours after eating.

If we have a few of these people because this was randomized or because it was blind, I can't remember. Actually, I don't know yet if they were included in the study or not. There were people like that who volunteered to do the study. If they end up to do the study or not, I don't know.

DR. COLLIN: Some half a year ago, we started a study where we looked at hydrolyzed products derived from wheat starch and the outcome of histology where we have also to take one biopsy before and one after a half year's period.

I did not have the feeling that the most

sensitive would not come. I think that those refuse to come who don't have a strict diet, because they feel that maybe their small intestine is not in a good condition, and the doctor will blame him or her about that.

Again, I would like to say that I suspect whether there are really highly sensitive people. Usually, when we start a study, we take 100 patients, and another 100 call to ask us, "Why can't I participate in this project?"

CHAIRMAN DURST: Okay. Marc.

DR. SILVERSTEIN: I have a question on a different area, so if there are further questions following up on this selection, then we should pursue that--?

CHAIRMAN DURST: I don't think so, go ahead.

DR. SILVERSTEIN: Could I ask Cynthia Kupper a question, if I may?

MS. KUPPER: Certainly.

DR. SILVERSTEIN: I was interested in understanding the extent to which a celiac

patient's likelihood of following up with a healthcare provider, physician or dietitian as opposed to a disease association or an informal network with regard to dietary advice, how that might be changed by more helpful information on food labeling?

In other words, if the labeling were more consistent, more trustworthy, more reliable, would there be increasing reliance on the labeling or the non-clinical advice, or would there be even more likelihood that physicians, dieticians and others would be able to be more effective in managing their patients? How would that likely affect patients' behavior, do you think?

MS. KUPPER: In many ways, it is two different issues. First of all, patients when they are diagnosed currently oftentimes they are referred to a dietician, but in many states dietician services are not paid for.

Consequently, many patients don't go, or, if they do go, the dietician is inadequate in preparing them with the information they need, so

they are very frustrated.

Referrals back to dieticians should happen, as suggested by the NIH Consensus Conference, because part of the problems with compliance is that they don't have that consistent follow up and they aren't monitored by a dietician, and there are some nutritional concerns about a gluten-free diet.

In a sense, it is a different issue. They need to be seeing a dietician, but they are just not referred or their insurance isn't going to pay, so they don't go.

Would a patient rely on labeling more than a medical professional like a dietician, if the labeling were more accurate? I really don't think so. I think they still need the dietician.

I think they will be happier being able to find sound advice from the labels, but it is still a matter of teaching them how to read a label, learning what the terminology is, and understanding that so they can make wise choices.

QUESTIONS FROM FDA: GLUTEN AND CELIAC DISEASE

CHAIRMAN DURST: All right. If there is no more general discussion or immediate questions for the speakers today, I would like to suggest that we start addressing some of the specific questions from the FDA, so that we don't run out of time at the end -- unless someone feels there is some other urgent question they want to bring up?

(No verbal response.)

CHAIRMAN DURST: Okay. The first one is the question of whether there is a distinct subpopulation of individuals with celiac disease and then going into the uncertainty factors involved in these measurements. Would anyone like to make some comments on that?

DR. KELLY: Ciaran Kelly. I think you can approach that question from two angles, one is easy to answer and the other is more difficult to answer.

From a clinical perspective, it is very clear that there is a broad range of clinical manifestations of the disease and that some individuals with celiac disease are able to ingest

the same amount of gluten in their diet as everybody else and don't demonstrate any clinical or nutritional ill-effects, at least in the short-term.

Whereas others, if they ingest a tiny amount of gluten, a crumb of bread, will have in a very short period of time a gluten reaction, a reproducible reaction that lasts a predictable length of time; so, clinically there are.

What is more difficult, however in mind is the fact that those clinical reactions don't predict the severity of the mucosal abnormality. At one level yes.

At another level there is also a variation we saw earlier, the Marsh classification, of the histologic abnormalities. There is a variation in that also, but they don't overlap neatly. You won't find always low-level lesions in silent patients. The answer is yes, I believe.

If you ask it either way, clinically and presentation, there is a huge spectrum histologically. Immunologically there is a

spectrum. It is just that they aren't always parallel.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Just to follow up, are they reasonably correlated, even if they aren't perfectly concordant?

DR. KELLY: I don't believe so. I will ask Alessio and --

DR. FASANO: I can't hear you.

DR. KELLY: You can't hear?

DR. FASANO: No. What was the question?

(General laughter.)

DR. BRITTAIN: We are talking about the relationship between clinical manifestations, immediate clinical manifestations, and I guess what you can observe in a biopsy? The people who are sensitive with respect to immediate reactions don't look the worst on biopsies? Is that what you're saying?

I'm asking are they fairly correlated? Could it also have to do with the length of disease? I would think the damage in the

intestines would be a function of a lengthy disease, whereas the short-term reaction had nothing to do with the length of disease.

DR. KELLY: Ciaran Kelly. As regards duration of disease, well we seldom have the opportunity to identify exactly when celiac disease develops, except in children who manifest symptoms. When an adult presents with celiac disease, it is impossible to determine the duration of disease at that stage. The other question is, Is there any correlation -- can you hear me?

DR. FASANO: Yes, I can.

DR. KELLY: Is there a correlation between histologic severity of disease and clinical manifestation of disease in terms of symptomatology?

DR. FASANO: The answer is no. It is pretty much a straight no. Keep in mind that the target organ of this autoimmune process is an organ that has 200 square meters of surface, so it is huge.

What do you define "severe" as? If you

define "severe" as 80 percent of the surface is damaged, then it may be that we can have that kind of correlation.

With our methodology right now, consider that maybe there will be a change in that story, but now with endoscopy we see the first few inches of this 14 feet.

It can be absolutely destroyed what you see. But there is absolutely no damage with many, many times patch lesions where we go with the endoscope, and these people are sick like dogs because it is everywhere, all the way, to affect a sizeable amount of the surface. Your processing and absorption and digestion of foodstuffs is dramatically affected.

That is the reason why there is no such correlation on the clinical ground versus the procedural ground, because the procedure cannot give you the full breadth of the damage of the intestines.

DR. COLLIN: May I comment?

CHAIRMAN DURST: That answer was given by

Dr. Fasano.

DR. FASANO: By now, because of the action probably you know who we are, right?

(General laughter.)

DR. COLLIN: Pekka Collin. If I may comment, I agree with Alessio that there is no correlation because we have some patients with very mild atrophy and severe osteoporosis, and then a flat mucosa without any symptoms.

However, there is one correlation. Our ultimate goal, if you look at who is sensitive and who is not sensitive, if you look at how the mucosa will recover, how is the mucosa recovery, if the initial lesion is very severe and the patient has remained undiagnosed for many, many decades, then their recovery is very slow. Maybe in elderly people it is seldom complete, but when the initial mucosa is mild, I think we achieve full recovery quite soon.

CHAIRMAN DURST: On that same question, I think we have to address the uncertainty factors and whether tenfold is sufficient using a safety

assessment-based approach. That is a reasonable uncertainty factor?

DR. MALEKI: What is the starting point?

CHAIRMAN DURST: Soheila.

DR. MALEKI: Oh, Soheila Maleki. I assume you would imagine what would be the starting point. If you imagine it would be 200 or 20 and then hitting the limits of detection for the methods at this point and whether you can detect it, if you go tenfold below 20, then I think you will surpass the methods of detection, whereas if you are 100 or 200, then you may be able to say that would be sufficient. I think will wait to see if the statisticians differ.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: This is Erica Brittain. It also depends, I guess, we have been hinting or talking about possibly having two levels, gluten-free, which would probably be pretty close to as low as you can go and maybe something that is not so strict.

Obviously, you would use a different

uncertainty factor there for the two levels. Again, it is the same discussion we had yesterday. The 10 seems very arbitrary. It also depends on which data set you start with. I mean, they all have limitations.

DR. GONSALVES: This is Dennis Gonsalves. It seems that a preponderance of data from all of the different presentations suggest that 20 parts per million for Canada and the various studies were really more or less agreed upon. At that level you don't get this reaction. If one looks at 20 and if one looks a the uncertainty factor, it looks like they licensed this at 20. If you have a tenfold uncertainty factor, well, this was 18. I think that there are data that suggest that --

DR. BRITTAIN: Two.

DR. GONSALVES: Yes. Ten percent up or down?

DR. BRITTAIN: Down. It would be two.

DR. KELLY: Go down to two.

DR. GONSALVES: Two, yes. Well, so this is five, so you can adjust that. Anyway, my

suggestion is that there really is pretty good information that you are very close.

You can argue all of these different exceptions, but at some point you have to decide whether this uncertainty factor of 10 is sufficient. I won't argue that based on what I have heard it is pretty sufficient.

DR. KELLY: Ciaran Kelly. In fact, I agree based on the data that is available, albeit limited and albeit imperfect but scientific data is always limited and imperfect, that it appears as though there is agreement around the general range that appears to be below a threshold for injury.

If there is broad agreement across the data, perhaps an uncertainty factor of 10 might even be considered excessive. I think there has already been a sort of de facto uncertainty factor enacted in going in other communities from 200 to 20, and that was largely based on concerns about whether or not the 200 was low enough. I would suggest it might be worth considering that.

Again, it depends on where you start. I

feel if you start at a conservative level below which the scientific data that are available suggest there is no evident injury, either by symptoms or by histology, then that may be a comfortable level without an uncertainty factor.

CHAIRMAN DURST: Okay. Marc and then Erica.

DR. SILVERSTEIN: Marc Silverstein. I would like to make a comment. It seems to me that in medicine we have lots of uncertainty and uncertainty from lots of sources. Some of the uncertainty comes from bias and some of it comes from confounding and some of it comes from measurement error.

It seems to me that the rationale for uncertainty factors that was applied to toxicology for environmental exposures in our discussion yesterday is we couldn't find a reasonable clinical or biological reason to think that level of that approach would be appropriate for IgE-mediated immune reactions.

It seems to me that although we have

learned or heard about the non-IgE, cell-mediated immune injury in celiac disease there is little rationale, from what we understand about the disease, to attach an uncertainty factor of tenfold or whatever-fold.

I understand how a public safety mechanism, it might be nice to have an uncertainty factor, it doesn't seem to be consistent with our understanding of either IgE-mediated immune injury or cell-mediated immune injury for celiac disease. It is kind of a comment.

For those who know more about celiac disease than the biology of immune-mediated injury, is there any reason to have a rationale for thinking that you can measure the variation in the response or the threshold for a response based on a factor, whatever the factor might be?

I don't know what body of understanding, whether from biology or medicine, would be applicable so we are using toxicology here. I would ask for some comment from those who study the immune response.

DR. FASANO: If I may? This is Alessio Fasano. We had a long discussion in '99 and 2000 when we were designing the study about what would be the biology readout, because that is what it really boils down to.

What would be a satisfactory readout to make us comfortable in saying the immune system, genetically skewed to react in not immune fashion, will be turned on by "X" amount of gluten? A study designed that should take three months took almost two years to reach a consensus, because there were different philosophies that were on the table. There were people that say clinical, serological, biochemical, histological, combination and permutation, all of the above.

The reality of the story was that we weren't on evidence-based on the retrospective studies done where some of the people that participated plus our other colleagues, and we realized, one, clinical was absolutely not reliable.

Two, the biochemical, the other antibodies

was also not reliable because we still don't know the role of these other antibodies, the pathogenesis.

We all agree, while there was some disagreement about the statement I just said, we all agree though that the final product of the autoimmune process, i.e., the autoimmune biological readout, is the damage of the intestine. That was the only confidence parameter that everybody agreed upon.

The reason why this was not a joke is because unfortunately, based on that decision, the only way they could make a statement in terms of biological readout implied two endoscopies. That in terms of study design was inartful.

I mean, not only do you have to go to somebody that is healthy who goes on a gluten-free diet and asks to have an endoscopy that he or she has no business to do, but then we heard this after three months. A wheat starch level is the only way to do it.

DR. SILVERSTEIN: Could I follow up with