food additive or a pesticide residue or something like that and dividing it by 100.

Classically, tenfold is for extrapolation from animals to humans, and tenfold is for intraindividual variation. Consequently, what uncertainty factor should we use?

(Slide.)

DR. TAYLOR: For allergens, since you have human subjects that can be used, the ideal thing would be to determine the no observed adverse effect level for specific allergenic foods among a human population that is allergic to that food, and then apply an uncertainty factor to get your threshold dose.

(Slide.)

DR. TAYLOR: To do that with any degree of confidence, you have to challenge a fairly large number of allergic individuals. You would have to identify the NOAEL for each patient.

You would probably also have to identify the LOAEL for each patient to prove the person is still allergic to the food that is under

consideration.

It would be good to determine the variation between individuals in NOAELs because it is probably a millionfold. A standardized protocol would be handy so that you didn't have uncertainty about the differences in protocols.

(Slide.)

DR. TAYLOR: There is no animal to human extrapolation needed for food allergy considerations because we have human data. We have already selected a sensitive subpopulation of the human population.

The question arises, Did we include the most sensitive individual? I think that is an important consideration for this panel. We have heard several speakers say, "Well, maybe we have not."

My argument is that perhaps in terms of representing the whole allergic population to a particular food we have actually excluded the other end of the dose distribution curve, and we actually have included a number of people from the most

sensitive subpopulation.

(Slide.)

DR. TAYLOR: I want to point to this study again. People have interpreted this study as a publication involving the dose distribution for the whole food-allergic group allergic to peanuts, eggs, and milk. It is not that; it is a study of the most sensitive individuals in clinical population.

(Slide.)

DR. TAYLOR: Well, how much data is out there? Is there enough data to make your decisions? I think there can be if you can wrestle with the uncertainty factors and the differences in protocols from one study to another.

I just went through what I think is the most relevant literature. Some of these are in your "FDA Report," which contains a big table at the back that somebody very laboriously put together. I think they actually found most of the relevant studies.

I congratulate them for that, because that

is not particularly easy to do. I went through those studies and added up the number of patients that are in each one of these studies that were subjected to double-blind, placebo-controlled food challenges and for which a published LOAEL exists.

Now, there are lots of differences in protocols, so there are uncertainty factors with how to plug this data into one of Rene's curves. What you can see is there are lots of subjects. This is for peanut. Note, I put an asterisk by our 2002 paper, and that is because that is not original data. Some of those patients may also appear in some of the other studies. We got concerned about whether to count them twice.

(Slide.)

DR. TAYLOR: This is for egg.

(Slide.)

DR. TAYLOR: This is for milk.

(Slide.)

DR. TAYLOR: We have got a lot of data points. What are the uncertainty factors? Well, you've got adults, adolescents, children, infants.

Many of the studies have been done on pediatric populations; fewer studies have been done on adults. You can do challenge trials on both of those. A lot of the diagnostic challenge trials are done on infants, but they are not done in threshold study types of experiments.

(Slide.)

DR. TAYLOR: You've got the problem with the nature of the challenge material and the allergen content of that challenge material. This is again from our 2002 study from Threshold 1.

You can see the number of different materials: ground peanut, peanut flour, peanut butter, egg white, dried egg white, whole egg, dried whole egg, and raw versus cooked for most all of those. Then, you've got whole milk, non-fat dry milk and even infant formula as the milk challenge materials.

In many of these cases, the physicians didn't determine the protein content of the challenge materials, so you've got to make glorified guesses. There are uncertainties about

the challenge materials.

(Slide.)

DR. TAYLOR: I would argue that studies should be compared using protein content. This failure to provide that data makes the evaluations really difficult. If the protein content of the challenge material was not determined or cannot be determined using reliable data in the literature, then the study probably has to be rejected from consideration by groups like this.

There are well-characterized challenge materials like non-fat dry milk, dried egg white and soy flour that I think you can assume what the protein level is based on standardized industry data. Thresholds should be established in terms that can be related to analytical methods like milligrams of food or milligrams of food protein.

(Slide.)

DR. TAYLOR: There are also issues related to blinding that Stefano already talked about. Some clinicians use labial challenges. They put a drop of the food on the patient's tongue or lip.

That is often used for young infants.

I think that is particularly difficult to interpret what the dose was. However, diagnostically it is good procedure, but otherwise it is kind of difficult to figure out what was going on. Then, there is the choice of dosages used for the challenges.

Probably the biggest uncertainty is this issue of the fact that most of the publications were done for diagnostic purposes, and so when you look at the published literature you get the LOAEL and not the NOAEL. I actually think a lot of the NOAELs are clinically available; they are just not published.

There is more uncertainty in using a LOAEL rather than a NOAEL to established threshold doses; there is patient selection criteria; exclusion of people on probably both ends of the curve; and there is variability in individual threshold doses.

Diagnostic challenges tend to report only the LOAELs; the NOAELs in some cases may not be recorded. As Dr. Wood pointed out to us in his

study, in many cases the patient reacted to the lowest dose administered.

However, if it was 400 or 500 milligrams, that is a pretty sizeable dose. I think there is a lot of uncertainty if you use that as your LOAEL to try to try and figure out what the threshold dose might be. You are much better off to focus on lower dose challenges where there is less uncertainty even if you have to use the LOAEL.

How far above the NOAEL is the LOAEL; and if using a LOAEL, how big should the UF be? I think that is the question that they wanted me to try to answer.

(Slide.)

DR. TAYLOR: I got bold and I did try to answer it. If the LOAEL is based on subjective symptoms, "My mouth itches," then I don't think we have to be very concerned about uncertainty factors, because in the limited experiences that exist in the literature there is a ten- to a hundredfold variations between the doses that begin to provoke subjective symptoms and the doses that

tend to provoke objective signs. I learned something today. I'll try to say "signs."

Now then, if you have a LOAEL based on objective reactions, what uncertainty factors should you use? Well, then I think you would need to have very careful expert analysis of the clinical study you are looking at.

I could argue that if you looked at one of these clinical threshold trials that have been done using microgram and low-milligram dose level, that you could use a very low uncertainty factor.

However, if you are going to rely on publications like Perry, et al., from 2004 where you only have data on the reactions that occur at the lowest diagnostic challenge dose and it is 400 or 500 milligrams, then you've got a much bigger uncertainty factor because you could be a long ways above the NOAEL.

I don't know what you would do in this particular case, so I put a question mark by it. I actually think those kinds of studies are not very helpful.

In fact, if you read Perry, et al., they don't tell you what the lowest challenge dose is. I just think they follow the standard protocol, and it is 400 or 500 milligrams. Obviously, if you had NOAELs, that would be better yet.

(Slide.)

DR. TAYLOR: Well, what about this patient selection issue? I think that is another key uncertainty. I'm not sure that the published diagnostic evaluation are representative of the whole population of allergic individuals.

Someone mentioned that this referral clinic bias, if the go to a referral clinic, then they are more seriously affected individuals in the first place.

Those are the ones that we tend to publish data on, and even we tend to publish data on individuals that are selected from that population because their history suggests they may react to lower doses.

I would say that the clinical threshold studies that are published in the literature are

distinctly skewed toward the more highly sensitive patients.

Now, have some people actually been excluded from diagnostic evaluation and clinical threshold trials? Yes. People with history of severe allergic reaction, people with histories of unstable asthma.

There is no way you can involve an unstable asthmatic in one of these trials; they will react to everything you do including the placebo. In all likelihood, the ethical thing to do is to see if you can get their asthma under control.

Some physicians exclude severely affected individuals, but I think it is discoverable to figure out how many. I think this panel needs to know the answer to that question.

Is that 1 percent of the population, 5 percent of the population, .1 percent of the population? I think that is discoverable, but we don't have the information.

(Slide.)

DR. TAYLOR: I present this information to you because I think it is very relevant. This is a paper from Scott Sicherer and Hugh Sampson and Hugh Sampson published a few years ago. I only picked out the soy allergic data from this paper.

It is a double-blind placebo. They purport data similar to that in Perry, et al. It is a double-blind, placebo-controlled food challenges of 53 soy-allergic people. I wanted to point out that 28 percent reacted to the first dose, which was 400 or 500 milligrams. Although, good luck figuring out how many it was 400 and how many it was 500; it is not in the publication.

Fifty-three percent reacted at some intermediate dose and 19 percent reacted at the final dose, which was either 2 or 2.5 grams or an open challenge with like 8 grams.

That tells you that there are a lot of individuals that are in these very high dose ranges, at least for soybeans, that is their individual threshold doses. We tend to focus on these people, but just remember this is 25 percent

of the population.

(Slide.)

DR. TAYLOR: Another deficiency with this paper is they don't tell you whether the milligrams are soy protein or soy flour, so I'm not sure. It is probably soy flour, but that is just a guess. Then, this is a study from the French group, Moneret-Vautrin's group. I just wanted to show this to point out that the levels, the individual threshold doses for individuals, can vary enormously in big, clinical trials. This was 103 individuals.

(Slide.)

DR. TAYLOR: Have they been severely affected? People have been excluded from challenge trials? Do they have lower or minimal eliciting doses? Do they experience severe reactions at very low doses? Or, are they simply individuals who have made big, dumb mistakes in their avoidance diets? I mean, I think that is a considerable possibility.

(Slide.)

DR. TAYLOR: This study was mentioned, Jonathan Hourihane's study. He took individuals with asthma and without asthma and those with food-induced asthma are more likely to have a severe reaction. That is pretty well documented.

You can see that there is not a big difference in threshold doses for asthmatics and non-asthmatics -- a little bit of difference down here, but it is not all that dramatic compared to the other uncertainty factors.

(Slide.)

DR. TAYLOR: Now, Wensing's study gets mentioned a lot, too. The thing I want to point out here is there are only five subjects in this study that had objective symptoms. For all of the others, Wensing, et al., stopped the study with subjective reactions, "My mouth itches." That is going to have a big impact on the minimal eliciting dose.

They did look at people who had histories of severe reactions versus people who had histories

of mild reactions. Remember, most of these are subjective reactions. You can see that maybe there is a 10- to 100-fold variation amongst these individuals.

(Slide.)

DR. TAYLOR: In conclusion, I would say that there is a lot of uncertainty factors. I think the biggest ones are the use of LOAELs versus NOAELs in the published information and the patient selection biases in these studies.

I do think we have a lot of information out there in the clinical literature, but whether that data is that of an appropriate form to allow a regulatory agency to make a reasonable decision, I'm not sure.

I do know that there is lots of clinical threshold trials underway around the world, that within a few years we will have more data done with a consensus protocol or some minor variation of that, and that might make some of this easier to interpret.

Thank you.

CHAIRMAN DURST: Thank you.

Are there any questions or discussion for Dr. Taylor?

(No verbal response.)

CHAIRMAN DURST: All right, I guess not.

Thank you, Dr. Taylor.

Marcia Moore has an announcement to make.

MRS. MOORE: I guess that is the hardship of going just before lunch as you said.

(General laughter.)

MRS. MOORE: For the public comment period that we have at 2:15, can I see a show of hands of the folks who are here right now for that and will be speaking. If you could stay when we break for lunch for about 5 to 10 minutes, it appears that several of you didn't get the full instructions. We want to go over the instructions with you for that.

That's all I have.

CHAIRMAN DURST: Okay. Thank you very much.

I guess if there is no further discussion

at this point, we will break slightly early for lunch and reconvene at 2 o'clock as the schedule indicates.

Thank you very much.

(Luncheon recess.)

A F T E R N O O N P R O C E E D I N G S

CHAIRMAN DURST: Before we begin our public comments, we have one final presentation, and that is by the lead author of the document that we are discussing today, and that is Steve Gendel.

Dr. Gendel is a senior scientist in the National Center for Food Safety and Technology of the FDA and he will describe the overview of approaches to establishing thresholds for allergens.

Steve.

OVERVIEW OF APPROACHES TO ESTABLISHING THRESHOLDS: ALLERGENS

DR. GENDEL: Thank you. I guess I would like to start by acknowledging that I am aware of the awesome responsibility that goes with being the first speaker after lunch.

(General laughter.)

DR. GENDEL: I am going to try and be quick before everybody has a chance to drift off. Also, the purpose of what I'm doing here, since the report has been out for several weeks and I'm sure

that everybody on the Committee has had a chance to review it in great deal, I'm not so much going to present an overview as a refresher or a reminder for you as to what is in it specifically today on the parts related to food allergens, with the idea of sort of setting the stage leading into the discussion for the Committee later this afternoon.

(Slide.)

DR. GENDEL: To start, what I would like to do is look at the purpose of the report, why we wrote it. This is important for the Committee to think about because the purpose of the report was to identify approaches that could be used to establish thresholds for the major food allergens and for gluten, with the emphasis on "approaches."

The report was not intended to make a decision about whether to establish thresholds or to choose an approach, and it was not aimed at discussing thresholds for individual allergens. We were interested in identifying the approaches that are available and looking at the advantages, the disadvantages and the data needs for each approach.

It is something to keep in mind when we look at what the contents of the report, the "Draft Report," actually are.

(Slide.)

DR. GENDEL: The overall organization is fairly straightforward. The mandatory introductory material which in this case put the report in context as to why we were doing this and how this relates to the FDA's mission, then there was a scientific review of what was known about food allergy and celiac disease, and then discussions of the approaches that they Working Group identified for establishing thresholds, so very straightforward.

(Slide.)

DR. GENDEL: In terms of the scientific review of food allergy, we considered a lot of factors, some of which are listed here and there were some others beyond this.

Two points I think to bring out are under the area of exposure. We did talk about the effects of processing on allergens, how that

affects both consumer responses to the substances and also we discussed the methodology related to the detection and quantitation of the major food allergens, and, again, how processing affected that.

Then, as Dr. Taylor mentioned, we spent some effort at trying to identify and discuss the clinical literature, the published challenge studies, which are the fundamental basis for any discussion of understanding how the allergic consumer responds to these foods.

(Slide.)

DR. GENDEL: In terms of the approaches that we identified, there were four of them that the Working Group identified: analytical methods-based, safety assessment-based, risk assessment-based, and the statutorily derived approach. I'm going to say a couple of words about each of these as we go along.

The analytical methods-based approach is, as the name implies, one in which any thresholds are established based on the sensitivity of the

methods available.

This approach is useful for those allergens where validated methods are available, but the Committee was cognizant of the fact that this method, this approach, is not linked to public health outcomes or public health concerns directly.

The safety assessment-based approach is one which we have heard a lot of discussion of this morning. In this case, it would involve using published values for LOAELs or NOAELs as the basis for establishing thresholds and applying uncertainty factors.

As we heard, the appropriate uncertainty factors would be dependent upon the gaps that were identified in the data, how much data was available, and what was contained in that data would determine what the appropriate uncertainty factors would be. This is an approach which has moderate data needs.

The risk assessment-based approach, on the other hand, is one which would use clinical response distribution data, that is, information on

responses across the whole spectrum of concentrations of allergen.

We were referring to this in the quantitative sense of quantitative risk assessments, where by the use of modeling and other techniques such as we discussed before, the approach could be used to derive quantitative estimates of risk and of the associated uncertainty at any particular level you might be interested in.

This is scientifically a very powerful approach, but it is also an approach which has the greatest data needs. Again, this morning we heard some discussion about what those data needs are and what the limitations of the available data are.

Finally, the statutorily derived approach, the statutorily derived approach is one in which thresholds are determined based on language that appears in a relevant law as promulgated by Congress which is then used to extrapolate thresholds from that language.

In the case of the FALCPA, there is language which exempts highly refined oils from the

labeling requirements, so the statutorily derived approach could be used the same based on protein levels in those highly refined oils. Those levels could serve as the basis for establishing thresholds in other foods besides the highly-refined oils.

This approach is also one in which the links between any potential thresholds and public health issues and public health outcomes is not clear, although it is an approach that could be used.

Based on the review of food allergy that was present in the "Draft Report" and based on the discussion of the approaches that we were able to identify, the Working Group came out with five findings related to food allergens.

The first one, which I think is an important point to make, is that whatever decisions are made regarding the establishment of thresholds and the approaches that might be used to establish thresholds and any thresholds that might be derived using these approaches need to be reevaluated

periodically and probably frequently as new data and analysis methods become available.

We heard a lot today about ongoing clinical trials, ongoing studies, developments and new methods, so whatever decisions are made now need to be reevaluated as these new data become available.

Secondly, the Working Group found that the analytical methods-based approach could be used to establish thresholds for allergens, if the validated methods were available.

However, we felt that if this method is used, it should be replaced by thresholds established using one of the methods with a link to risk and public health as soon as that is possible.

The Working Group found that the safety assessment-based approach is a viable approach for the major food allergens using published LOAELs or NOAELs, using a standard of the initial objective symptoms in clinical trials as the basis for determining LOAELs or NOAELs, and, as I mentioned, appropriate safety factors which would be

determined by analyzing the literature.

The risk assessment-based approach is, obviously, potentially the strongest scientifically of the different approaches. We realize that this approach is one which is just now being applied to allergens for the first time, and we still feel that there is a need for more data and more analysis of the appropriate assessment tools, modeling tools, and ways of analyzing the data at this time.

Finally, the statutorily derived approach could be used to set thresholds, but based on the levels of proteins that are found in the highly refined oils it is possible that this approach would provide thresholds which are unnecessarily protective of public health.

We felt that the Working Group felt that if this approach was used, that the results should be reevaluated again as soon as possible when the data became available on the methods for using one of the risk assessment-based approaches for establishing thresholds.

That is, briefly, the reminder of what is in the report.

QUESTION-AND-ANSWER SESSION

CHAIRMAN DURST: Are there any questions or comments for Steve at this point? I'm sure we will involve him in our discussions later.

Yes.

DR. BRITTAIN: This is Erica Brittain. I want to commend the group together that put together the report. It is really easy to read and very interesting. One part of it that I found a little confusing that I didn't really understand was the analytical method.

Am I correct or not in understanding that to be basically the level of detection? If something is below the level of detection, it would be considered a threshold, or have I misunderstood?

DR. GENDEL: Yes. Basically, as I said, the idea was we were trying to identify all the available approaches. As we mentioned in the report, there are some examples where effectively a threshold has been set at the level of detection of

the methods available.

DR. BRITTAIN: Thanks.

CHAIRMAN DURST: Anything else for Steve while we've got him up there?

(No verbal response.)

CHAIRMAN DURST: Okay.

DR. GENDEL: Thank you.

CHAIRMAN DURST: Thank you, Steve.

I guess now we can get into the public comment part of our program. We have a number of speakers lined up. Just as a reminder, each speaker will have three minutes, and then the hook comes out.

(General laughter.)

PUBLIC COMMENTS

CHAIRMAN DURST: There will be additional time for questions beyond the three minutes. Okay, our first speaker will be Tracy Atagi from the Food Allergy Anaphylaxis Network.

MS. ATAGI: Hello, my name is Tracy Atagi. I am actually not from FAAN, I'm a member, but I'm speaking here for myself. I am a mother of a

six-year-old boy with a severe peanut allergy.

I am speaking here today because I have four specific concerns with the methodologies that are discussed in the draft paper. Due to time constraints, I will try and summarize these briefly, but I hope the Committee will also consider my longer written statement.

My four concerns are, first, the draft paper fails to consider sensitization as a health endpoint of concern. Second, the oral challenge data are unacceptably biased, because they are likely to only represent the least allergic individuals excluding not only the most sensitive individuals but also your average allergic individual.

Third, contrary to the findings of the "Draft Report," the use of initial objective symptom is not generally protective.

Fourth, the proposed methodology for the statutory based threshold does not meet minimum data quality requirements. The data on oils with no detectible protein were arbitrarily excluded and

the data on protein levels that were included in the paper appear unrelated to highly refined oils.

The issue of sensitization is important because without sensitization there is no food allergy. Parents of children with a family history of food allergies are advised to delay introduction of allergens to help the immune system develop fully.

When I read labels, I read it both for my allergic son and also my, hopefully, not allergic daughter. For my son, it is a matter of life and death. He has had an anaphylactic reaction. I hope never to see that again.

However, it is also in a way a matter of life and death for my daughter, because if delaying introductions of an allergen can keep her from developing that food allergy, then the risk to her life is greatly reduced. Thus, I would urge the Committee to consider sensitization as a possible health endpoint for the health-based methodology.

Apart from the issue of sensitization, the safety assessment-based threshold contains serious

biases. The "Draft Paper" explains that the oral challenge study data are used for diagnostic purposes, but fails to reach the obvious conclusion.

Individuals who would volunteer for these studies are those whose initial diagnoses are in doubt. In other words, these individuals who are volunteering are likely to be the least allergic in the population, not only are the most sensitive individuals like my son not included but also your average allergic individual.

This bias is compounded by the recommendation that the threshold be based only on the initial observable symptom -- I'm sorry, objective symptom.

As the draft paper notes, a particular dose could result in mild symptoms on one day and life-threatening reactions the next. Excluding data on subjective symptoms is unprotective, given the range of reactions even within the same individual.

Finally, the methodology on the statutory

derived approach is fatally flawed. The draft paper offers no evidence that the oils examined in the study are highly refined, and the decision to exclude all oils with no detectable protein appears arbitrary.

Frankly, I would assume that oils that have no detectible protein would be the only ones that would meet Congress' intent in exempting highly refined oil. Instead of using protein levels in different oils to define the threshold, FDA should use the lack of protein in an oil to define whether it has been highly refined.

Thank you very much.

CHAIRMAN DURST: Thank you.

Are there any questions or comments?

(No verbal response.)

CHAIRMAN DURST: Okay. Well, we will move on.

Our next speaker is John Carroll of the Enzyme Technical Association.

MR. CARROLL: Good afternoon. I am from the Enzyme Technical Association. I am the current

chairperson from that group. As you can tell from the title of the association, this is about enzymes, which are Mother Nature's wonderful and ubiquitous tools.

I wish to thank you for letting us, allowing us, to give a brief presentation here today. We also wish to thank and compliment the Committee and the FDA for this effort here. Anybody who is at all looked at any of this stuff, and we have tried for a year or two, this is a complicated, complex area, a full gamut including emotion. This is a very difficult task that you have, but we know that our FDA is up to it.

We are going to talk about where enzymes fit and the view of the Enzyme Technical Association. We put this in a question-and-answer type modality.

Our first question is, Where do enzymes fit within the scope of allergen labeling as defined by FALCPA? Our answer, after quite a lengthy period of trying to evaluate this is, no, they don't fit.

After reviewing FALCPA, after looking at the "Draft Report," which is excellent, plus a multitude of allergen literature, we have come to the conclusion that enzymes do not fit, and here is why.

Enzymes are not proteins within the Big 8 allergens. Some enzymes, but not all, are manufactured using fermentations in which raw materials obtained from one or more of the Big 8 are used to feed the microorganism from which the enzymes are extracted.

Enzyme products obtained from fermentations are not directly derived from the Big 8 list. They are derived from microorganisms fed on media that may include protein from one or more of the Big 8 list.

Furthermore, enzymes are normally purified to remove the biomass and to achieve a certain concentration. Why are we here today? is our second question. Why is the Enzyme Technical Association here today talking to the Committee?

Well, the Enzyme Technical Association has

been asked whether enzymes need to have allergen labeling, because the enzyme industry uses some of the Big 8 allergens for enzyme production, as I explained, as food for the microorganisms.

While ETA is convinced that FALCPA never intended to regulate the labeling of enzymes, as an as association we are prepared to share the information we have collected to support our conclusions.

We would also like to point out in the form of a question, What is the policy of other regulatory bodies in the international arena? The United States, like every country, tends to think we are the center of the world; it is not true.

There are other people who, as we have heard today, have addressed this question. They have actually addressed it also specifically in the case of enzyme products.

The U.S. needs to understand that both the EU and Japan, the regulatory bodies in those countries, have concluded that enzymes are not required to have allergen labeling.

CHAIRMAN DURST: Your time is up. Can you conclude?

MR. CARROLL: This is the last point.

Indeed, the European Commission Health and Consumer Protection Directorate has clearly stated that enzymes are outside the scope of their Directive 2003, which was November 2003, a similar directive, very similar to FALCPA.

Thank you.

CHAIRMAN DURST: Well, I have a question as far as the enzymes. Are they used in a way that they can be considered a food? Are they in a form that is eaten, or are they just used then as a method of processing?

MR. CARROLL: They are used as a method of processing. As it sounds like you're aware, they are used to catalyze reactions, biocatalysis. They are used as processing aids. They are used at levels, like any catalyst, that are very low.

Roughly, the enzyme protein in a normal process would be at a maximum of 1 part per million of the enzyme protein itself. Part of the nature

of that is the nature of biocatalysis that they use at very low levels.

CHAIRMAN DURST: Okay.

MR. CARROLL: No, they are not an ingredient. They are not part of the food, per se; they are processing aids.

CHAIRMAN DURST: They are purified so that initially they have small amounts of any potentially allergenic proteins, and then in addition they are used in even smaller quantities in the processing, or they come through in--?

MR. CARROLL: If you step through it, the first thing is any allergenic protein that might be part of the raw material used, of the fermentation that is being used, is food. The first thing is it is consumed.

We are trying to make enzyme protein. Just like you and I at lunch are trying to make hair or skin or human protein, we are trying to make enzyme protein. That is our business; and if we don't do it, we lose.

Then, the next step is we are talking

about purification of the biomass of any residue non-enzyme protein material because that is our interest is that enzyme activity.

Furthermore, if you look down, it is the way a biocatalyst is used. They are used at very low levels and that is why they are not typically ingredients. They are processing aids to achieve a reaction, to achieve an effect. They are not in the final product for a purpose --

(Simultaneous discussion.)

CHAIRMAN DURST: Do you perceive that there would ever be a situation where their level of allergenic protein would be at a point where they would be considered an allergen in a food?

MR. CARROLL: We have looked, and that's why we said we are willing to talk with FDA about our overall analysis. However, the levels that we are talking about are orders of magnitude below anything we've heard today.

CHAIRMAN DURST: Okay.

Did you have one?

DR. MALEKI: Yes.

Just a comment as far as I know, to the best of my knowledge, they haven't been reported as allergens, enzymes that are used in processing. Most of the allergens are pretty well characterized -- well, not necessarily characterized but groups of enzymes or proteins that fall under that category of allergens have been recognized.

As far as bioprocessing, I don't think, and one of the clinicians can probably comment on that, but I have not heard of a reported reaction to something like that.

MR. CARROLL: We have looked into the literature, and there are no cases of enzymes as food allergens. They are not basically food allergens. They are ubiquitous.

DR. MALEKI: In foods, I realized that they are used very ubiquitously. I think if there was a reaction, that they probably would have been reported.

MR. CARROLL: Also, in the apple -- actually if you eat some nice, raw vegetables today, you were taking in all sorts of DNA and

enzymes, that is where we are at. We are just actually using Mother Nature's tools for specific applications.

Anything else?

DR. KELLY: Yes, a question.

MR. CARROLL: This is great (laughter).

DR. KELLY: Do you want to make the point that enzymes should be outside of the exemption standards?

MR. CARROLL: I guess the easiest way to capsule it is out of the scope of FALCPA. It is not intended to be part of it, because we are not ingredients.

DR. KELLY: You would prefer not to engage in the notification process?

MR. CARROLL: Right, I mean, I don't think it is actually appropriate in this case.

DR. KELLY: How does that differ from sharing your data with the FDA?

MR. CARROLL: Well, we can share it in terms of showing them how we got to this conclusion.

DR. KELLY: Isn't that what the notification process consists of?

MR. CARROLL: No. I think in this case it would be more appropriate to be ready to meet with them to show were we are. I think it is so straightforward that it is not -- that would be a misuse, I think, of the system.

DR. KELLY: Yes.

MR. CARROLL: I mean, they are going to be very busy getting this right. From what I see -- and I've actually tried to study this also personally, taking it as a hobby, it is quite a fascinating area -- this is a hard job. I think it would be disingenuous to use even the administrative system for such a case.

CHAIRMAN DURST: Could you put some information together for the Committee as far as these points that are being raised? I think at this point we are getting off track, and we want to get back onto the main thrust of our work, and that is, the consideration of the different approaches for setting the thresholds.

MR. CARROLL: Right, I agree.

CHAIRMAN DURST: Thank you very much.

MR. CARROLL: You're welcome.

CHAIRMAN DURST: All right. Our next speaker will be Diane Castiglione from the Food Allergy Anaphylaxis Network.

MS. CASTIGLIONE: Good afternoon. My name is Diane Castiglione. I promised myself I wasn't going to do this (weeping). Oh, well.

My 13-year-old son is allergic to milk, eggs and wheat. While I know that gluten is the subject for tomorrow's hearings, I should also note that I have celiac disease and maintain a gluten-free diet.

My son's allergies were diagnosed shortly before his first birthday. The message from his allergist was clear. He must avoid all foods containing milk, eggs and wheat. This task is even more daunting and challenging than it sounds, especially given the prevalence of milk and wheat in food products.

Fortunately for me, Michael was so young

that he had barely started to eat table food. I was able to do my research before I introduced new foods to him.

Since his initial diagnosis, a lot has been accomplished with regard to food allergy awareness, and I have been pleased to see the voluntary efforts made by food manufacturers with respect to identifying allergens on their labels.

However, at the same time the hodgepodge of labeling methodologies create a confusion for those of us who depend on the accuracy, clarity and transparency of these labels (weeping).

When a product that my son has been eating for years without any problems suddenly begins to carry a "may contain" statement, more questions are raised in my mind rather than less.

Has there been a change in the ingredients or in the processing? Has the allergen always potentially been present in the product without my knowing it? Or, the skeptic in me wonders has nothing changed, and the statement merely reflects a lawyer's concerns about potential lawsuits? I

must make the difficult decision of continuing to purchase the product or removing it from my son's already limited diet.

I cheered when the new labeling law was passed. At last some rationality and clarity would be established so that I could read food labels with confidence. My life would be simplified at least a little.

However, the subject of this hearing raises doubts in my mind and makes me uneasy. How will these thresholds be established? What will it mean if an ingredient falls below the threshold levels? Will manufacturers begin to implement their own set of statements resulting in a hodgepodge similar to that which exists today? How am I then to interpret those statements?

When I told my son about today's hearing and asked his opinion, after all he is the one who lives with allergies, he told me that if an ingredient list on a product that he consumes suddenly included something to which he is allergic, while he might regret having to give up

the product, he would not have a problem doing so as long as he knew that the label was based on established fact.

While we know that the medical and scientific communities have not yet established specific universally applicable thresholds, I think my son's comments raise two key points about this process.

The process of establishing thresholds must be transparent. The thresholds must be clearly defined so that all manufacturers are held to the same standard. The question of how to handle products in which the allergen falls below the threshold must be addressed in order to avoid the development of inconsistent disclaimers on packaging such as currently occurs.

Food labels are our lifeline. We depend on them for the health, safety and well-being of our children and ourselves. When reading a label, there should be no doubt in our minds as to its veracity and accuracy.

There should be no doubt in our minds as

to the motivation and rationale behind any statements regarding the ingredients and/or the processing of the product.

There should be no doubt in our minds that we are consuming a product that is safe for us. If the new law does achieve its desired effect, we need to ensure that its implementation does not replace one state of confusion and distress with another.

Managing food allergies on a daily basis is challenging. Please help us to take a step closer to reducing that challenge and to make the lives of those with allergy simpler and therefore richer (weeping).

Thank you for your time.

CHAIRMAN DURST: Thank you.

Any comments or questions?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

Our next speaker is Barbara Desa from the Food Allergy Anaphylaxis Network.

(No verbal response.)

CHAIRMAN DURST: Okay. She is not here, so we will move on.

Will Duensing?

(No verbal response.)

CHAIRMAN DURST: Let's see, I don't have his affiliation.

Bunge Milling on behalf of the North American Millers' Association.

MR. DUENSING: Mr. Chairman and Committee Members, thank you for this opportunity and good afternoon. My name is Will Duensing, and I am director of Quality Assurance and Technical Services for Bunge (pronounced Bun-gee) Milling, a large dry corn milling company with mills in the United States, Canada and Mexico. I am also here today, however, representing the North American Millers' Association as chairman of the Technical Committee.

"NAMA," as it is called, is a trade association representing the wheat, corn, oat and rye milling industries in the U.S. and Canada. NAMA's 48 members operate 168 mills in 38 states

and Canada with aggregate production of more than 160 million pounds per day of milled products or about 95 percent of the industry capacity.

As Anne Munoz-Furlong and several previous speakers pointed out in their presentations this morning, it seems to me it would be to us a disservice to the allergenic population if products that clearly have shown a long history of safe use would be labeled as containing allergens due to unrealistically low thresholds as a result of FALCPA's requirements or regulations.

At issue in our industry is the presence of trace quantities of soybean protein, which may be present from the country in milled corn and other cereal grain products.

While the establishment of thresholds is obviously critical to the practical application of FALCPA regulations, these thresholds should not be unduly or unnecessarily restrictive to the allergic person's food choices.

In that regard, we offer these following comments. First, these thresholds should be based

on the best possible scientific data regarding the effect of an allergen on the allergenic individual and certainly these thresholds should not be set at zero.

Secondly, the use of analytical-based methods would appear not to be appropriate as this approach is very likely to result in a threshold which would be unnecessarily low.

Additionally, FDA should probably avoid the establishment of artificially low thresholds with the "intent" of adjusting them later. Historically, this has not taken place despite good intentions. Additionally, any future adjustments would prove to be confusing to the consumer and disruptive to the food industry.

Finally, FDA must provide a clear timetable for the establishment of these thresholds. In our opinion, they must be prepared to provide financial support for studies where critical gaps exist in the current database.

Thank you for the opportunity to offer those comments.

CHAIRMAN DURST: Thank you.

Committee, any questions or comments?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

Our next speaker is Martin J. Hahn from Hogan & Hartson.

MR. HAHN: Thank you. My name is Martin Hahn, and I'm speaking on behalf of the Grocery Manufacturers Association, and I do have financial ties to the food industry and that association.

GMA and its member companies have been actively involved in the allergen issue. Indeed, GMA was one of the instrumental agencies or instrumental associations that was responsible for the development of the voluntary allergen labeling guidelines that Mark Nelson mentioned earlier. Those guidelines have resulted in the use of common English names on food labels well before FALCPA was passed.

The established of allergen thresholds is integral to the effect of enforcement of FALCPA.

FALCPA suggests incidental additives such as processing aids to the allergen labeling requirements. This exemption becomes problematic when the allergenic protein in a food is present at such low levels that it does not pose a risk to human health.

For example, typical uses of soy lecithin can result in levels of soy protein from soy lecithin in a part per billion and part per trillion range. These foods have been consumed by consumers without incident.

The legislation will fail the food-allergic community if it results in allergen labeling of foods with inconsequential levels of protein from major allergens.

Given the time limits for today's presentation, we offer the following brief comments, which we do intend to supplement with written comments at a later time.

With regard to the statutorily derived approach, we agree with the Agency assessment that it would be appropriate to develop interim

thresholds using a statutorily derived approach.

FALCPA specifically excludes highly refined oils from the definition of major allergen. Highly refined oils do contain small, yet detectible, levels of protein, which evidences a congressional recognition that it is appropriate to exempt from the major allergen definition products that contain very small levels of protein.

GMA believes the statutorily derived approach would support the establishment of 10 ppm as an interim threshold level. We note that many in the food industry have used this 10 ppm level for years as an informal threshold for food allergen labeling, particularly when it comes to processing aids.

We previously provided FDA with marketing data demonstrating that the presence of undeclared soy lecithin, fish gelatin, wheat starch contributing 10 parts per million of less than major allergenic proteins did not result in a measurable increase in allergenic responses over baseline.

We have reviewed the published literature and identified studies reporting various levels of proteins in highly refined oils. This review has identified that some oils have levels of 48 parts per million while some of them have less than 20 parts per billion.

Because highly refined oils do have varying levels of protein, we believe it would be appropriate to set the threshold at 48 parts per million, a level that is present in oils.

While we believe that may be appropriate, we would advocate the establishment of 10 parts per million as the interim level, because that is the level that is in the midway point of allergenic proteins found in products.

With regard to the method of analysis approach, we believe it would be inappropriate to se the threshold on the basis of validated methods. We only have one validated method, and that is for protein.

We also are concerned that as new methodologies become available there will be

ever-increasing sophistication of the analytical method which sets a number which is constantly changing.

CHAIRMAN DURST: Your time is up. Thank you.

Any questions or comments?

(No verbal response.)

CHAIRMAN DURST: Okay. Thank you very much.

Our next speaker is Ann McKay from the Food Allergy Anaphylaxis Network.

MRS. MOORE: Next.

CHAIRMAN DURST: The next speaker is Peggy Mockett from the Food Allergy Anaphylaxis Network.

MS. MOCKETT: Hello, my name is Peggy Mockett. I am the mother of Alexander, a 10-year-old boy who has life-threatening food allergies to tree nuts, peanuts, and corn. He is also allergic to soy, penicillin, latex, and has asthma.

I have administered epinephrine to him

during one of his anaphylactic reactions. My son has gone into anaphylactic shock before, experienced anaphylaxis three times, and managed through reactions involving skin rash, vomiting and hives

Two of my son's anaphylactic reactions and four of his milder reactions were due to labeling issues. We have been seen by five doctors, and all five instructed us to completely avoid his allergens. We were advised to decline food challenges to his major food allergens.

It was stressed and has been experienced that the smallest amount can cause a serious reaction in our son. There is no room for error for us. We have a rule that says you read it once, twice, and then again before you eat it. If you cannot read it yourself and I didn't make it, don't eat it.

Unfortunately, reading the label is not always enough. There have been times when ingredients were omitted because it wasn't considered a significant amount of the total recipe

or it was simply done in error.

Shopping for skin, hair and food items is a lengthy process. You must read each item every time and more than once, because mistakes are not an option for us. Even with perfect disclosure, ingredients change and must be checked.

Toothpaste is risky, because flavoring is not a detailed ingredient. Medicine flavoring is especially difficult, because pharmacists don't always know the added ingredients and the type of flavoring is not specific.

We are sometimes told, "It is not crucial to the product, so don't worry about it." We have to worry about it. Our son reacts quickly to minute amounts of his allergens. For him buying prepared foods is no longer an option.

Our past labeling issues have made it impossible. Even with flour and cream cheese, I have to call the manufacturer to be certain that the details are accurate.

I cannot imagine allowing someone who doesn't fully understand my son's individual

situation to determine at what level he will or will not have a reaction, a decision that could take his life. Setting threshold levels at anything higher than zero would be tantamount to playing Russian roulette with his life.

Thank you.

CHAIRMAN DURST: Thank you.

Any questions or comments?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

Our next speaker is Kim Mudd, Food Allergy Anaphylaxis Network.

MS. MUDD: Good afternoon. My name is Kim Mudd. I am a nurse at University of Maryland, and I am also a research study coordinator. I am on the Program Committee for the Food Allergy and Anaphylaxis Network.

I have been working with food-allergic patients and their families for over 14 years. I think I have performed thousands of food challenges. The integrity of food labels is important to the FDA, and it is important to the

U.S. consumer.

For the food-allergic consumer, the food labels are part of a life-and-death decision. When a patient is diagnosed with food allergy, they are counseled to read every label of every food when they buy it, when they serve it, and when they eat it.

If a food label contains an offending food protein, they are told to avoid it completely. This results in extremely limited diets with significant impact on basic nutrition.

The precautionary labeling terms such as "may contained" or "processed on the same line" force families and patients to contact manufacturers to try to gauge the risk of certain foods or to avoid them all together. As a rule, most of our patients and families decide on a zero tolerance approach, resulting in even more dietary restrictions.

If we are going to try to address the current confusion in labeling with threshold levels, we have a significant amount of serious

work to do. We do not have enough data to discuss NOAELs or LOAELs. The studies that have been done absolutely exclude extremely allergic subjects.

No one wants to do food challenges on somebody with a history of anaphylaxis. If you doubt this, ask yourself, "Would you sign a consent form that listed 'death' as a possible risk?" Could you sign that form for your child and let me feed that child, your food-allergic child, a food that you know has caused anaphylaxis in the past?

If we do ultimately end up with threshold levels, I need to know what to tell my patients and my families. We know that the severity of reaction and the dose required to elicit these reactions varies from person to person.

We don't have the data to tell these families what to expect. Food labels are the only tools that food-allergic consumers have to keep themselves and their children safe. If the food-allergic consumer loses faith in the integrity of these labels, they will be left with a very dangerous practice called "trial and error."

Thank you.

CHAIRMAN DURST: Thank you.

Any comments or questions?

(No verbal response.)

CHAIRMAN DURST: Thank you very much.

Our next speaker is Kim Mulherin from the Food Allergy Anaphylaxis Network.

MS. MULHERIN: Good afternoon. My name is Kim Mulherin, and I have an 11-year-old daughter named Courtney who is severely allergic to milk protein. Courtney's CAP/RAST test for milk is greater than 100, always has been. Since her limit exceeds the upper limits of the test, we cannot determine the exact numerical measurement.

Scratch tests for milk cannot be performed on Courtney, since the test itself poses too great a risk for someone with such a high sensitivity. The severity and the reality of my daughter's milk allergy goes far beyond theoretical numbers collected year after year.

Instead, her allergy is a very real day-to-day struggle where the seemingly simple and

necessary act of eating presents continuous, life-threatening dangers most people don't ever have to experience.

The prevalence of milk products in our society not only as the main ingredient but also as a filler or flavor enhancer makes avoidance especially difficult.

Since prepared foods and restaurant dining is essentially off limits, the accuracy and clarity of ingredient labels is critical for Courtney's well-being and safety.

Despite our very best efforts to avoid milk ingredients, Courtney has suffered severe anaphylactic reactions from ingesting both undeclared and minute amounts of milk protein.

In one instance, Courtney suffered an anaphylactic reaction when she was given turkey breast luncheon meat which, unbeknown to her caregiver, contained a very small amount of caseinate which was later discovered as one of the last ingredients on the label.

On another occasion, Courtney suffered an

immediate and violent reaction when she ate simply one bite of shrimp from a precooked package of shrimp cocktail purchased in a grocery store. There was absolutely no mention of milk protein on the label.

When subsequent tests and patient history ruled out the possibility of a shrimp allergy, the remaining contents of the store-bought shrimp which caused the severe reaction was sent for analysis to Mount Sinai Hospital.

The analysis revealed that the shrimp contained undeclared caseine and whey. To this day, none of the parties involved in the chain of production admit adding milk to the shrimp.

Just as Courtney's IgE level to milk protein is too high for the CAP/RAST test to measure with exactness, it is very possible that her immune system is indeed more sensitive than any laboratory test devised to predict a reaction. Courtney's sensitivity to milk is so high that we simply don't know what her safe threshold level is. Without this knowledge, any minimum threshold level

established by the FDA is nothing more than a statistical estimate.

Unfortunately, Courtney has already learned the hard way that a statistical estimate is far from a guarantee. Statistically speaking, since 80 percent of the approximately 3 percent of milk-allergic children outgrow the allergy by age 5, Courtney has managed to fall into the 6/10ths of 1 percent of children with a lifelong, anaphylactic milk allergy.

It is simply unconscionable for the FDA to ask such a person to bet her life on statistics rather than facts. When I explained to Courtney that the FDA was considering establishing minimum threshold levels, she anxiously replied, "Now I won't need to use an EpiPen after almost every meal."

Can you look her in the eyes and tell her with absolute certainty that she is wrong? That is the real minimum threshold level you need to establish for Courtney and every other person with severe food allergy.

Thank you.

CHAIRMAN DURST: Thank you.

Any comments or questions?

(No verbal response.)

CHAIRMAN DURST: Our next speaker is Kim Sclarsky from the Food Allergy Anaphylaxis Network.

(No verbal response.)

CHAIRMAN DURST: Our next speaker is Linda Webb from the Food Allergy Anaphylaxis Network.

MS. WEBB: Hello. I am Linda Gabel Webb. Thank you for giving me this opportunity to talk to you and for trying to do the right thing for people with food allergies.

I have food allergies. They are not too terrible, but I do have to avoid apples, pears, onions and garlic so I don't have asthma all the time. Naturally, they are my four favorite foods.

On a more serious note, my five-year-old son is allergic to peanuts, nuts, shellfish, and less so to seeds. His numbers are all way up high,

so that he actually can die from eating those things as opposed to just being itchy or wheezing like me.

The first time we figured out that he has this problem was when he almost died when peanut butter cookies were being baked in the house. Thank goodness he didn't eat them.

Once we found out, which was when he was about two, we have practiced complete avoidance to the best of our abilities by reading labels, and so on, cooking from scratch. We have been very fortunate that he has not had any incidents since then.

I actually am so strict that I don't even allow these things into the house, and I don't eat them myself, even though I'm not allergic to the same things because I want to be able to kiss him without killing him.

I have really come to count on some of the big food manufacturers who for a long time have voluntarily done this labeling, and I think very well.

I wish they would put "May Be Manufactured in the Same Plant" way up top in huge letters rather than at the bottom, but I really take that to the bank.

We have been very fortunate, and we are very grateful to them for that. I am looking forward to labeling getting even better and more thorough as it does become mandatory.

I have also tried to thank them, where appropriate, when I call their 800 numbers and talk to people and get further information about things like flavors, like one of the other mothers mentioned.

I am very grateful, and I don't buy their product (laughter). It is kind of a mixed blessing for them. However, I do have even greater confidence when I see that same company's products not having those ingredients listed.

One final note personally in addition to the life-threatening aspects of his allergies, my son, Charlie, who is five -- I'm not sure if I mentioned that -- also has a developmental disorder

that makes it very difficult for him to integrate socially with his little peers.

You know, I can't tell you how much it means that he doesn't have to be different in one other way at school where mothers that want to support him and support me can look at the list and know that he can have this brand of Fig Newtons and everybody else can have that, too, for a snack.

You know, it doesn't take away from the fact that he is "different" or that he has got his big, red emergency kit with him all the time, but it is just one way for him to fit in.

I have complete faith that he is going to continue to learn and grow and have a great life. My main concern is keeping him alive. Obviously, anything that the industry can do to make that more possible I am very grateful for.

Thanks a lot.

CHAIRMAN DURST: Thank you.

Any questions or comments?

CHAIRMAN DURST: Okay. We will move on to our next speaker, Jupiter Yeung from the Food

Products Association.

DR. YEUNG: Good afternoon. I am Dr. Jupiter Yeung, and I serve as the principal scientist for the Food Products Association in Washington, D.C. FPA represents the food industry on scientific and public policy issues.

Protecting the public from health risks while maintaining a viable food industry in an open society is a daunting task. The "Draft Report" provides a reasonable perspective of pros and cons of various options towards establishing allergen thresholds and helps to keep the public informed of the deliberative process.

While the report is a reasonable view of conceptual options for establishing thresholds, FDA should also consider the recent European Commission directive of providing a temporary three-year exemption for certain food ingredients derived from major allergens such as fish gelatin.

This directive was based on the scientific opinion of the European Food Safety Authority that these food ingredients are extremely unlikely to

induce an allergic reaction.

While an avoidance diet remains to be the most effective, too, for the allergic consumers, it is generally that there are threshold doses for allergenic foods.

Clearly, sufficient data are available to conclude that thresholds for certain major allergens are finite, measurable and above zero. Hence, the assumption of zero tolerance for food allergens places an unnecessary and unachievable burden on the industry.

The declaration in labels of all perceivable levels of major food allergens including biologically insignificant amounts will cause confusion to allergic consumers.

For example, small amounts of soy lecithin can be used as a releasing agent during processing but is not included in allergen labeling under the current requirements. Some allergic consume who previously had been safely consuming this product will unexpectedly find the same allergen declaration on this product as they expect to find

it in other soy-containing products.

Unfortunately, this is likely to put the sensitive individual in the position of either further restricting their food choices or choosing to ignore the label information.

Risk management is vital to the protecting the well-being of allergic consumers. Clearly, decisions must be based on current available knowledge, even with less than perfect and complete information. Without information on thresholds, it is difficult for the industry to optimize their quality control efforts to protect allergic consumers.

A reasonable certainty of no harm standard should be applied towards establishing threshold levels. It is not intended to ensure nor is it possible to ensure safety with absolutely certainty, and it does not mean that no individual under any conditions would be protected from any harm. Therefore, uncertainty factors that are reasonable should be applied, and only when needed, based on the relevance of the available data.

CHAIRMAN DURST: Your time is up.

MR. YEUNG: Pardon?

CHAIRMAN DURST: Your time is up.

MR. YEUNG: Can I make another minute.

CHAIRMAN DURST: Not another minute, but one more sentence.

MR. YEUNG: Okay. For example, the uncertainty factor is not necessary for intraspecies for peanuts because more than 10 of the studies were done in both male and female and also in adults and children.

Neither should a standard uncertainty factor of 10 be applied to the sensitive populations, since children and sensitive subjects were included in the clinical trials.

Since the lowest, not the mean, dose for an objective symptom is being used to estimate thresholds, an uncertainty factor of 2 may be justifiable to give added protection to the highly sensitive subpopulation.

Thank you very much.

CHAIRMAN DURST: Thank you.

Any questions or comments?

(No verbal response.)

CHAIRMAN DURST: Did we miss anyone as far as the public statements?

(No verbal response.)

CHAIRMAN DURST: We are scheduled for a break after the public comments. Even though we are a bit early, we will take the break and reconvene at 3:15. That will give us almost 20 minutes.

Thank you.

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

COMMITTEE DISCUSSION:

REVIEW OF THE CHARGE AND QUESTIONS FROM FDA

CHAIRMAN DURST: I would like to reconvene our session.

All right. This is the section of our meeting today where the Committee can, I guess, ask questions of any of the speakers that have presented earlier, and also discuss any of the main thrust of this. I would just like to establish a

couple of ground rules.

We had slightly gotten off track at one point today where we had gotten into labeling. This is not the purview of this Committee to decide any issues on labeling nor is it the purview of the Committee to try to come up with numbers as far as threshold values.

We are here to basically assess the report that the Threshold Working Group has put together as far as approaches and give our learned opinions on the report itself.

You have in front of you or everyone should have the charge to the Committee. I will just read the charge to begin with, and then we can get into the actual discussions.

The Food Advisory Committee is being asked to evaluate the "Threshold Working Group draft report, "Approaches to Establish Thresholds for Major Food Allergens and Gluten in Food." The Committee should advise the FDA whether the draft report is scientifically sound in its analyses and approaches and whether the draft report adequately

considers available, relevant data on major food allergens and on gluten. In addressing these issues, FDA requests that the Committee consider the following specific questions.

Now, again, for this afternoon, we are going to focus on the allergens. Tomorrow, we will be on gluten. You have in front of you some general points that we should consider and then some questions that the FDA would like our opinions on.

At this point, I would like to open up the discussions to the Committee, if there are any of you that still have questions for any of our previous speakers or would like to make some comments or statements about your opinions on this.

Yes.

DR. BARACH: Yes. Jeff Barach with the Food Products Association. I would like to commend the presenters this morning, but I have questions for Dr. Wood and Dr. Taylor. Both reported on the composition of the challenge studies in a different manner, and maybe they can clarify this a little

bit.

In Dr. Woods presentation, he said that the most allergic patient was not in his studies. Yet, Dr. Taylor reviewed many studies and said, yes, the sensitive individual is included and had an explanation of why. I thought that perhaps one or both could address that issue?

CHAIRMAN DURST: Dr. Wood had to leave early. I hope Dr. Taylor is around.

Yes.

DR. TAYLOR: Well, I think I can answer for both of us because I think I understand Dr. Wood's point of view as well. It is an individual clinician decision as to which subjects in a clinic would be subjected to diagnostic challenge trials.

In the United States, it has now become the practice that only challenges will be done on those patients who are below the 95 percent cutoff level for the CAP/RAST, at least in some clinics. That very well could be true in Dr. Wood's clinic at Johns Hopkins, I am not entirely sure.

On that basis, he was correct in saying

that the most highly sensitive individuals would not be subjected to challenge because in the U.S. you cannot get by ethics forums.

In Europe the situation is different. There are groups that challenge on a diagnostic basis every patient that they encounter as part of their standard diagnostic practice, at least that's what they tell me. That seems true from the publications that they have put in the peer reviewed literature.

Consequently, I think it varies from clinic to clinic, investigator to investigator, and report to report making the work of your panel even more difficult.

CHAIRMAN DURST: Yes.

DR. MALEKI: Dr. Taylor, Soheila Maleki, USDA. Can you comment on the soy lecithin? We heard a lot about that in the questions and comments. I was wondering if you know of any allergic reactions to that?

DR. TAYLOR: Yes, I have actually looked pretty carefully at the clinical literature on soy

lecithin reactions. I should start by saying that some highly respected clinicians like Hugh Sampson do not advise their soy-allergic patients to make any attempt to avoid soy lecithin.

Soy lecithin is acknowledged to contain residual protein at levels that might be somewhat debatable but probably in the range of 100 parts per million.

You would use soy lecithin in direct ingredient applications where it would appear on the label anyway because it has a functional effect in the finished product at 1 or 2 percent. You are talking about 1 or 2 parts per million soy protein, if you started with 100. In these processing aid applications, the levels would be several orders of magnitude below that.

There are two reports in the clinical literature of allergic reactions to soy lecithin, both of them involve both pediatric cases from Europe, I think both of them are from Europe, involving infants exposed to -- I know in one case it is soy formula and I think the other case is the

same.

Unfortunately, in my view, we don't know the protein level of the lecithin because the clinical investigators used an inappropriate method. They attempted to determine the protein level of the lecithin using the Kilnaught (phonetic) procedure which would pick up the nitrogen and the phospholate fractions. They got huge numbers, but the numbers are not valid in my opinion.

DR. MALEKI: All right, thank you.

CHAIRMAN DURST: Yes.

DR. KELLY: I just want to return, briefly, to the issue of challenge studies, which is important I think because they may well be used to determine acceptable levels.

My question has to do with an individual who doesn't need a diagnostic challenge study, because the clinical presentation is so clear. Are they included, in general, in the challenge studies? Secondly, individuals with very severe reactions, anaphylactic reactions, would they ever

be included in challenge studies or are they almost by definition excluded?

DR. TAYLOR: I think that there are clinicians in Europe who tell me that they challenge every potential food-allergic patient that crosses the threshold of their clinic. I'm taking it on faith that is true.

Certainly, if you look at the list of symptoms that their patients present with when you read their papers, that would appear to verify the fact that their challenging everyone or nearly everyone.

There definitely are clinicians in both Europe and the United States who do not choose to challenge subjects who have had life-threatening reactions in the past.

As I alluded to in my comments, I think that it would be very good to know what percentage of the referral patients fall into that category. I mean, we have heard from the parents of some of those children this afternoon.

I have to respect the clinical judgment of

those physicians. If they don't feel comfortable doing the challenge in their office, then that is the way it ought to be.

It is only the specialized clinics that challenge these severely affected ones. However, I don't know what percentage, even of these referral clinics, are excluded from challenge. That it discoverable, it is just that the question hasn't been asked.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Just a quick comment. I think there are still some clinics, of course like you said it would be wonderful to know the percentage, of the clinics that do this type of work and the percentage of the allergic individuals.

I do know some clinics and especially hospital settings and research places that do actually challenge people that do have anaphylactic reactions as well. Particularly in like one of the anti-IgE studies, I know that they used patients --

(Simultaneous discussion.)

DR. TAYLOR: In the immunotherapy studies, I should have pointed that out, were these anti-IgE studies, the Tannock study and others. They have tried to actually enroll people who have very severe peanut allergy into those trials. They wanted to find out if the therapy had any benefit, and that would be the best group to make that judgment.

CHAIRMAN DURST: Okay. Any more questions for Dr. Taylor while he is up there?

(No verbal response.)

CHAIRMAN DURST: No? Okay.

Yes.

DR. BRITTAIN: I have just kind of a big-picture question. Is that appropriate now?

CHAIRMAN DURST: Sure.

DR. BRITTAIN: It is going to more a comment. It is really hard for me to think about this without defining what the goal is of the threshold is in very precise terms. Are we talking about a threshold where only 1 in a 1,000 of very sensitive people would react? Are we talking about

a threshold where 1 out of 100 all allergic patients would react? Without specifying that, it is really hard to talk about what the threshold should be.

CHAIRMAN DURST: Yes. Well, there again we are not talking about what the threshold should be, it is how to best determine it.

DR. BRITTAIN: I don't see how you -- I don't mean the actually --

CHAIRMAN DURST: Value?

DR. BRITTAIN: Yes, I don't mean the value. Like, later on when we talk about uncertainty factors, I don't see how you would go through that exercise without establishing what your goal is of the threshold, not what the threshold value is. I don't know whether we should ask the FDA that or--?

CHAIRMAN DURST: Steve, can you address that or--? Steve is in consultation.

(General laughter.)

DR. BRITTAIN: It just strikes me that is the first step.

CHAIRMAN DURST: Yes, in some ways this is like a bootstrap operation. How do you get to a level without knowing what the level is?

DR. GENDEL: This is Steve Gendel for the record. I guess all I can say is we are not at a position to really address the question that you have raised.

In the terminology we use, that is considered a risk management decision that would take into account the scientific information and the kinds of analyses in these reports and other factors in making that decision.

Right now, we are simply interested in trying to identify the approaches that could be used. Once a decision is made on whether to establish thresholds and which approaches to use, then we would be in a position to get to the kind of specifics that you are asking for.

DR. KELLY: Let me ask a related question, then, if I may. Assuming that whatever methodological approach one took, one would arrive at a certain threshold level where it would be a

0.1 or a 0.01 percent risk of a significant event.

There will still be individuals who fall outside because of being highly sensitive, because of their situation at the time, unpredictable events that are outside of the curve or at the very far end of the curve.

Is there a mechanism to also accommodate those events or to gather information about those events in an anecdotal way? Can that ever be considered to be part of the methodology? For example, for drugs we have reports, very rare events, of drugs.

People make reports, and at certain points the reports mount to the level where there is a pattern. We may only be talking about 12 individuals, but 12 individuals who died, and a drug may be taken off the market. Have you considered any approach like that?

MR. GENDEL: I think that is one of the things that we have asked you to discuss, so I'm just going to turn that question back on to you.

(General laughter.)

MR. GENDEL: We would like your input on how we should go about thinking about those questions.

CHAIRMAN DURST: Yes. I think it is farther down the line where we have to -- and probably this Committee won't do it -- I believe EPA, for example, uses the term "acceptable risk," an with these parents behind us I am sure none of them would say that there is any acceptable risk, that this has to be very safe for everyone.

In reality there is the economics and many other considerations that come into this. Again, this is not something that we have to consider during our deliberations today, but we want to get into the approaches that are. DR. GENDEL: The one other point I think I would like to make, as I mentioned, one of the things that we are trying to do is to evaluate the advantages and drawbacks data needs of each of the approaches. Clearly, questions like that are relevant to making those evaluations.

CHAIRMAN DURST: Carol.

DR. WASLIEN: Carol Waslein. I would think any kind of approach should include a mechanism for establishing new methods, new guidelines once data becomes available -- not just saying once data becomes available but some kind of mechanism that says "Now data is available."

Whether that is effects or symptom reports or it is the results of clinical trials that are underway or whatever that is, it might be that our stance or position here is to say "Do this when this becomes available, do this when this becomes available." This would set up a system for evaluating ongoing cases, for evaluating data that must be available in the trials but was never reported. That could be part of our approach.

Because the approach gives us a choice of four, and I personally like choices of 1.5, 2.5 or a combination thereof for the approaches because it says go back and look at safety data.

Well, can't you set a standard based on existing safety data now and not have to go back and look at it, if safety data exists? You use a

combination of approaches and a mechanism that also says at a given time we will go back and look. When a certain amount of test data becomes available, you go back and change it.

CHAIRMAN DURST: Yes, Suzanne.

DR. TEUBER: I actually have a question for Sue, for Dr. Hefle, and this relates to the fact that in the data that has been presented on LOAELs and NOAELs, of course most of these challenge studies were done in diagnostic settings where, as you were pointing out, not all of the patients with severe, severe, life-threatening allergy would have been included at all; they would have been excluded.

When you have been involved in some of these threshold studies that are designed for this purpose of safety assessment, some of the studies that were mentioned like Dr. Wensing was the lead author on, in those situations then the studies were stopped with the subjective symptoms before any objective sign.

This actually would bring up the fact that

the studies that you are involved in would add a number five approach, because it would be a modification of finding three of the safety assessment approach.

Right now, it is written as a suggestion to use objective signs for the LOAEL. The data that you have, you have actually been able to recruit more patients with a history of severe, life-threatening reactions.

It seems to me that if we were to suggest yet another approach, the one that you have outlined may be very appropriate. I am wondering if you can comment on the recruitment of these patients to us? This might help address this great concern that people with severe anaphylaxis aren't included.

I'm thinking that the adults that I know, I have hundreds of adults with severe, life-threatening tree nut allergy. They are eager to participate in threshold challenges, if they know that it would be stopped at their first symptom of any tingling in the mouth. That is

their usual symptom in the real world. They would be happy to participate. I think I would like to hear more about your recruitment.

DR. HEFLE: Well, I have to give a lot of recognition to my European collaborators, because I've got to say that this is way easier to do in Europe.

They have patients beating down their doors to do this that are severely allergic, even parents offering their children up because they have a greater sense of the greater good over there in comparison to American people I think in the later respects.

They will have a lot of recruitment. It is easy to recruit because they are told exactly what will happen and they are told exactly that they will stop with these mild reactions.

Now, Dr. Wensing, they made a decision that they were going to stop at that level, but not every physician makes that same decision. I just let the physicians make the decisions. I don't have patients, so I'm not qualified to make those

decisions as to when to quite a challenge.

Actually, the people that do participate, we have found in the last couple of years that they find thresholds beneficial to their day-to-day maintenance.

Carsten Bindslev-Jensen will give talks about how he uses thresholds in educating his patients. He says he has two patients with the same IgE levels and things, same size skin tests, one can eat half an egg and one can't have any at all. The advice you give is much different and the restrictions you can have in one versus the other are much different.

We see more and more people actually seeing if they can be in these challenges and wanting to do them and feeling pretty comfortable. Now, that is not to say it is necessarily really easy to go find 300 people to do this and especially for soy and some of the other allergens where we have a challenge.

However, we have gotten some fairly severely allergic people to participate. They felt

comfortable but they have to feel comfortable with their physician and comfortable that the right precautions are taken. I can understand why someone would not want to do this.

Yes, it is really individualistic as to when the physician is going to stop. As a physician, I'm sure you can understand when you make that kind of judgment call, too. It is based on years of experience and thousands of challenges, and not everybody is comfortable doing that.

I hope I've kind of addressed your question. As I said, it is a lot easier to do this in Europe. They seem to take the whole population in there versus the United States.

Here, it seems much more difficult to get people to do this, to make them feel comfortable that this is going to be okay, and that they will be able to go through it and not experience really adverse reactions.

DR. TEUBER: I think it would be actually easy to get people here. Like I said, I have hundreds of people who have expressed interest in

this sort of thing with severe, severe allergy, but it wouldn't be for a diagnostic challenge. It would have to be in the research setting.

DR. HEFLE: Right.

DR. TEUBER: Therefore, it would be laid out that it would be stopped at the most mild symptom. This brings up another point, then. If you stop at that mild symptom, can you trust the results?

I believe in those studies they used two active and two placebo for each. Are you familiar with any data that that has not been a correct assumption for stopping a challenge?

DR. HEFLE: I am not aware of any other data that is an incorrect assumption. That was their approach, and I decided to let them go with it because they know better than I do.

Perhaps, other physicians with other research would approach it a different way, but I am not aware of any other data that would impact on that or would show that is, indeed, the right way to do it.

DR. TEUBER: I would just note for the record, for those of you not involved with food challenges, Dr. Allan Bock wrote an office manual on food challenges that was published back in, I think, 1978. In there for subjective symptoms, it was suggested that multiple challenges be done to make sure that it was a "real reaction."

During the same setting period, once somebody has had, say, a symptom of itching in the mouth, then it would be blinded as to whether the next challenge they had was again an active one or placebo, but you would repeat this several times.

In practice, we use this for instance when somebody is concerned that a headache may be triggered by food, or it can be used in this setting of coming up with a threshold. For something like headache, it would have to be done on multiple days.

Rather than just doing one active and one placebo, there are multiple given. I am, again, hopeful that the multiple challenges that were done you could get more people as you did with severe

reactions to help establish a threshold.

DR. HEFLE: It would be nice. At our last threshold conference in Majorca we had 20 clinicians who do this from around the world sitting around. A lot of them felt that if you had a subjective reaction, you actually should go to the next one to get an objective reaction because they are usually pretty mild at that point, too.

They felt as a group not every single time that it might be a necessary thing to actually go beyond the mild, subjective reaction when you are trying to get a threshold study done. That was kind of the consensus of the clinicians.

DR. TEUBER: Thank you.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: I have a couple of issues that I think are important to clarify our thinking, but I'm not sure how they would specifically be addressed, so let me mention the issues and then maybe you can see. It is related to the whole issue of testing.

In clinical medicine, we often use tests

that are not perfect, but they are pretty good. Some of the tests we use, the tests themselves are not a gold standard.

If we want to test for anemia, we would test for a hemoglobin and say we know what anemia is because we define it by the absolute value of the test. However, there are many other tests which are for conditions that have some other criteria for the diagnosis.

We can set a threshold for the test, and we often do set a threshold. When we set the threshold low, the test may be more sensitive and less specific; and when we set the threshold high, it may correspondingly differ.

It seems to me we have a choice with using symptoms, subjective findings, and signs, objective findings. With a symptom, we may be more sensitive and less specific; and with a sign, we may be less sensitive. Did we get that correct?

DR. TEUBER: Mm-hmm (affirmative response).

DR. SILVERSTEIN: It may be less sensitive

and more specific. I believe that there is some inferences we can make from the existing literature about how a food challenge may perform as a diagnostic test for the presence of food allergen.

The caveats and questions there, though, Does the test perform in the general population the same way it performs in the studies that are published? Of course, it may or may not perform as well, depending on whether there is some selection bias.

To the extent to which published literature tells what the selection was or the reviewers for the report can provide that information, we would be able to be more or less confident that the tests and the inferences about the thresholds are strong.

In that regard, some guidance might come from the study I believe the Agency for Healthcare Research and Quality funded a study to evaluate systems for evaluating the strength of evidence.

I think Kathy Lohr and the Research Triangle Institute was responsible for that. They

set sets of criteria questions to ask when looking at a question that would be answered by a randomized control trial, by a case control study, a cohort study, or a diagnostic test.

I think the report might be strengthened a bit if we could look at some of the criteria that was proposed by that study for looking at diagnostic tests.

As I looked at it, most of the issues that they covered were considered by the FDA in the report, but it might be useful to look at that, which is out in the literature. It has been out now for a couple of years.

The second thing I want to do is to clarify our thinking from how a test may perform to diagnose the presence of food allergy so that a clinician and a parent or a patient can together decide what is a course of treatment, from the prognostic value of what would happen in the future in the real world when the patient's family or the patient tries to adhere to dietary restrictions.

The question we would have is, What is the

prognostic value of a positive or a negative food challenge test? If, for example, we were to accept either symptoms or signs as our threshold, in those patients who are positive in symptoms or signs reproduced and a diagnoses of food allergy is made and the clinician says, "This is what you should do for your diet," what is the future risk and occurrence of subsequent episodes of anaphylaxis, since we know some of those patients will indeed experience episodes?

In the patient who is reassured that, no, they don't have a food allergy because they did not react positively to a food challenge test, do we have literature about how reassuring that is? In other words, does the negative food challenge test provide sufficient assurance of future risk for those patients?

I suspect there is very sparse literature. However, if there were some literature that looked at long-term outcomes in food challenge test positive and food challenge test negative individuals, we might know whether the thresholds

used in the test for those individuals could be used to set policy.

DR. TEUBER: I can partially answer that. In terms of if somebody has a negative challenge, you are getting back again to using food challenge as a diagnostic measure not for risk assessment in somebody you already know has an anaphylactic sensitivity to foods. It is really kind of a separate thing.

In that situation, we would do an open challenge with the food as they would normally eat it because what was used in the challenge setting, and Steve Gendel did write about this, may not reflect what is really consumed by the patient.

For diagnosis, it is still different than having someone you already know who has anaphylaxis to food. That is where I'm thinking that the possibility of using the subjective symptoms for your LOAEL may be very reasonable, because we also talked about how there are other factors that may influence somebody's reactivity on a particular day.

Asthma I think was brought up, alcohol, inflammatories, exercise, even the time of year. Some people may have more histamine-releasing activity in terms of their mastocytes and basophils after the spring pollinosis season, if they also are highly allergic to pollen. Those factors could go into that uncertainty factor.

If you then say that you are only going to accept objective symptoms from the data, that means a lot of Wensing's data on threshold would actually have to be thrown out, because only 5 patients out of the 29 or so actually had gone up to objective signs.

This was one of the few studies where because these patients were told, "We're going to be extremely safe, extremely careful, and we're going to stop before you have anything severe," they were able to recruit the people with anaphylaxis that we want to protect by recommending a safety assessment approach here.

I mean, that is why I keep bringing up this issue about can we accept that for the issue