of safety assessment, if you have blinded challenges that are repeated.

I think it is a really different issue than diagnosis and different than the performance of food challenges as how reproducible they are. I'm not enough of an epidemiologist or a risk assessment person to go into that. I'm looking at this from the patient care viewpoint. Does anyone else want to elaborate? Actually, anyone out there can, too.

DR. SILVERSTEIN: Well, so let me ask, then, if we were to use symptoms, which is more sensitive, and you had an individual whose parents and the physician recommended a food challenge and the food challenge test was negative, no reaction or symptoms, and you knew what the threshold was, then that would be sufficient to make recommendations, or then the person might get an open food challenge?

DR. TEUBER: I'm sorry, that person would actually not have a negative challenge because, again, to be included in a database that would be

adopted by the FDA for determining a threshold, the person who had a negative challenge in the studies would not be included.

See, you have to be getting up to a response, either a subjective response that is reproducible or to something objective, lip swelling or nausea or vomiting or something else. You wouldn't even include that individual in your evaluation.

DR. SILVERSTEIN: There would be a population of food allergy patients who may have a negative test but might yet have the diagnosis of food allergy?

DR. TEUBER: Again, they may be someone who has developed tolerance now, and so they would be challenged openly for food as they would normally eat it. If they can eat that, then they no longer have a food allergy. Or, they may be somebody with a special situation such as exercise-induced anaphylaxis that is food associated where they only have a reaction in a certain context.

CHAIRMAN DURST: Comment?

MS. HALLORAN: I think that Dr. Teuber, though, is getting to an important issue, which is a concern that I had listening to all of this testimony, which was that the repeated issues as to questions that the data on LOAELs and NOAELs just is not that good.

It is better for peanuts and eggs and milk. However, in the other categories, though, everybody was saying that the data is really not sufficient. I'm interested in Dr. Teuber's suggestion of actually recommending to FDA that possibly they could conduct some research to establish NOAELs and LOAELs. She proposes a methodology that appears to possibly get around some of the medical issues.

DR. TEUBER: None of this is my proposal. This is all proposed by people already doing it. Again, a lot of these studies are underway right now. I take absolutely no credit. You are looking at some of the people over there who are doing these studies.

It is just that the studies designed specifically for this issue, there area a few that have been mentioned that were done in this way or they are underway right now.

There hasn't been any funding to do them. For instance, for tree nuts there is only one on hazelnut, and none of the other nuts have been addressed at all. We see Dr. Hefle nodding her head over there.

Again, just to be recommending some approaches right now, I think a hybrid approach of a 3.5 of accepting the LOAELs for some of these subjective reactions might be very reasonable, but then I guess some other methods will have to come in for those foods not covered at all.

MRS. MOORE: I'm sorry, I want everybody to remember to say your name.

DR. TEUBER: Oh, I forgot to say my name. Suzanne Teuber.

MS. HALLORAN: Jean Halloran, sorry.

MRS. MOORE: Okay. For the transcriber, she can probably pick it up with the voice. Okay,

do you remember to say your name.

DR. TEUBER: I'm sorry.

DR. KELLY: Just a follow up briefly.

CHAIRMAN DURST: Your name?

DR. KELLY: Ciaran Kelly, sorry. A brief question about this issue of positive result on challenge or maybe more specifically a negative result on challenge. Then, it is frequent that there would be a real life challenge with regular food?

DR. TEUBER: Yes.

DR. KELLY: How often would the real life challenge would be positive where the laboratory clinical challenge was negative?

DR. TEUBER: That sort of data is, indeed, in the literature and in some of the literature that Dr. Gendel has cited here, some of the follow-up studies by the Johns Hopkins group.

Unfortunately, that statistic is not on the top of my head, so I would be venturing, but certainly there are folks -- and in Dr. Bock's series as well -- who tolerated the dehydrated food

in challenge and then reacted upon eating the real deal. I can't give you a percent.

Again, those folks would not be included, their data would not be included for this sort of risk assessment that we are really trying to decide on approaches for them here today.

DR. KELLY: It clearly speaks to the validity of one of the tests that they've used to establish a threshold.

DR. TEUBER: Again, the people that would be used -- this is Suzanne Teuber again -- the people who would be, hopefully, enrolled in studies to establish a threshold would be those who very clearly have had anaphylactic reactions or a range of reactions that very clearly is to the food in question and where a diagnosis has already been established. It would not at all be to use just data from diagnostic challenges.

A diagnostic challenge, I think most people would want to go to an objective sign when you are trying to figure out a difficult case, like, is it sesame or was it the peanut in the

Asian food in this 34-year-old who has a new onset of allergy?

You think it's probably sesame, because most peanut allergy has its onset in childhood, but you would really want to be sure because that really determines which food is this person going to avoid, sesame or peanut.

In that case, as a physician, I would want to go for a mild, objective sign rather than stopping for a symptom. Again, that is a different issue than trying to give advice to the FDA of which approach to choose for labeling.

CHAIRMAN DURST: Yes.

DR. MALEKI: Soheila Maleki here. It seems to me like with all of the methodologies that have been outlined in this report that everybody seems to be looking at or interested in the threshold of those studies.

I think it is pretty much a consensus out there that the threshold dose studies need to be done, and that would be the practical approach to go about determining this somewhere down the line.

That seems to be the most important I think to establish as far as the patients go.

On that line, I would like to ask Dr. Hefle if she could tell us how they would go about this and how long does it take?

I think it seems like, and of course this is my opinion in this case, that before you can take any methodology to determine, say, "Okay, this is the limit of detection of our analysis," well, our technology is so high that our limit of detection can be down to 1 molecule.

In other words, you can probably find peanut dust on this (pointing) tablecloth, if you wanted to. Therefore, at this level we can't say the limit of our detection is going to be what is going to establish this. It is going to have to be human studies.

DR. HEFLE: You are asking about your average threshold study? How long does it take? What is required?

(Simultaneous discussion.)

DR. MALEKI: Yes, how long does it take

and how much money.

DR. HEFLE: Yes.

DR. MALEKI: How do you get the money? what do you do? what is limiting? and so forth.

DR. HEFLE: Nowadays, 29 patients for an allergen you can find pretty easily like peanuts, at least $200,000 U.S. dollars. That primarily is clinic cost and hospital cost.

The hospitals are charging more. They have costs. They have to have a crash cart ready; they have to have nurses ready; they have to have a lot of things ready. Therefore, in most cases, we do this in research centers, so a lot of that is clinical cost. That is the vast majority of it.

We have to make standardized materials and send these to everybody. We have to find the patients and make sure they are the right kind of patients.

For something like soy, it is one of the "Big 8" allergens and there are a lot of kids out there allergic to soy, but they are all mostly infants.

To find 29 soy-allergic people, which we are trying to do right now, for our soy threshold study is pretty daunting and we have to go to the ends of the earth to try to do that.

It can take from concept to actually getting the challenges done and getting through the ethics board, maybe two years. Depending on the ethics board you are dealing with, they might take six months to get an approval; it is very individualistic.

Denmark has got two ethic boards they have to go through, so if we hope to get any patients in Denmark, they've got to go through twice as much and get translated in Danish and all sorts of extra things.

But even just developing the food vehicles in a double-blind manner and doing the sensory analysis in the studies we need to make sure that it is truly blinded and available to clinicians. To test 29 patients can take easily 6 months to a year to develop the correct vehicle, choose the right representative food to use. It can easily

take two years even for a really great allergen we can find lots of patients for.

Then, the funding, there is no governmental funding for this to date. All of the funding to date for threshold studies, I've gotten a little bit of USDA. Steve and I have gotten a little bit of USDA funding out of this. The food industry has paid for the majority of these studies to date because they really want the answers, so that is where the funding comes from.

It is kind of difficult for them to identify funding for this, too, rather than just throw "May Contain" labeling on the products. You know, what is the choice here? For some companies, it is easier to say, "I'm not going to cough up $50,000 to help you. I'm just going to put labeling on my products."

We have gotten a lot of support from the food industry, and we are moving ahead as best we can. It has been kind of slow in getting this data out. We need a consensus protocol before we can move ahead.

There are some centers in Europe that are choosing to go ahead and do some threshold studies and kind of work that in, if we provide the materials, as they can without having a huge amount of financial support from us, as they can work it into their patients, if they are truly interested in it.

For a specific study, it probably will take at least two years for any one allergen and at least $200,000. Those costs are just going to continue to go up. One clinical investigator that I like to use a lot in Europe just told me that now they are required to have insurance for the study, and that is only going to be $10,000 U.S. dollars for this one study. And that is only for about three patients. We will have to do another $10,000 the next time we want to do a threshold study. It is getting more and more costly to do.

CHAIRMAN DURST: This is Dick Durst. I would just like to pick up on one comment that Dr. Maleki made concerning the sensitivity of the analytical methods. It is true that for a great

many of the allergens we are talking about, we can get down to very low levels.

We don't want to get into the situation that we had with the Delaney clause with carcinogens. At one point you set a level based on the state of the art, which may have been parts per million, and the law says, "Well, as much as you can trace or detect, that is the limit."

The analytical methods got better and better, and it got to parts per billion and trillion and quadrillion. Therefore, the analytical methods, per se, probably are not the way we want to establish a threshold. However, you do need the analytical methods, then, to verify that the foods that the thresholds are set on actually conform to it.

I think, again, we have to keep going back to these challenge methods, you know, the actually biological studies to set the threshold, and then the analytical methods can provide the validation.

DR. MALEKI: Soheila Maleki. I agree with you a hundred percent that we definitely need the

analytical methods once the thresholds are established or a range is established in order to determine if we can comply with that -- in other words, compliance -- but I don't think that alone they could be used in that way. Since, as you instructed, we are supposed to be evaluating some of these methods, that is the point I was making.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. I would like to follow up on the "N" equals 29 patients for a modest size study. That would be assuming that the hypoallergenic formula, or a percentage of 10 percent, was an appropriate prevalence of a reaction in the population of generally allergic individuals that you are testing.

However, I think we need to say -- it is different for us to say that we believe that only 10 percent or fewer than 10 percent of patients like those tested will go on to experience an episode of food allergy, which could be of very different severity even if only a third were

severe.

I think we need to say the sample size in power calculations to have meaningful assessments are as a risk that is probably important to patients would be much greater, orders of magnitude greater.

In Dr. Luccioli's handout, there is a slide where the top row is 10 percent, which then equals 29 for a 95 percent confidence interval. The bottom line, as I can read it, is "1/5,000" or "1/10,000." We might want to have very high levels of confidence, more than 95 percent, if the true rate may be less than 1/1,000 or 1/10,000 who would have such an event. I do think that you are being very optimistic, and even so will just be confident about a rate of 10 percent.

CHAIRMAN DURST: Okay. Petr and then Margaret.

DR. BOCEK: Petr Bocek. I have actually one question and one comment. Regarding the analytical methods, I absolutely agree that we do need them. We talk about 1 part per billion or

million. What is that part?

I would like to know the analytical method. Does it relate to the major allergen, let's say, RH1/RH2, polyclonal serum ELISA? What is the physiological relevance? I'm missing that point as far as the analytical methods.

DR. HEFLE: Well, the analytical methods were not originally designed to find the allergens. That wasn't the purpose of the food industry. They wanted to find out, Do they have peanut, or do they not have peanut? It is claimed? Is it not claimed? In that case, then, it is not necessary and when we are designing these to look for the allergen specifically.

In addition, not every allergy is known for every food yet, either. If you target just one, you could miss the rest of them. The approach that has been very successful is to use polyclonal serum, a more crude extract in general, and they seem to work very well at picking up peanut/no peanut.

The parts per million varies from kit to

kit as to what it really means. It can mean parts per million peanut, which is the whole food. What does that mean? It can mean peanut butter or whatever.

In some cases, the companies will say that means part per million peanut protein. What that means is the soluble proteins from the peanut that can be detected in an aqueous situation. That is one of the debates about what these numbers mean when they are crunched out at the end. What is it expressed in? How do you relate that to other test kits? That is a challenge. However, they are not specific for the allergens.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek again. There was a comment, which was a clinical comment, which relates to point number three on the food allergens of the charge, which is basically asking whether if we have any specific data for one of the major eight allergens, if it can be easily transferrable to others.

Obviously, that is not an easy answer, but

we know from clinical studies as far as development of tolerance, outgrowing actually a food allergy, there are significant differences between these eight groups, specifically peanut stands out.

Frequently, kids who outgrow peanut allergy, which current studies show it is up to about 20 percent, still retain their high levels of specific IgE, which is absolutely not true for milk and egg.

At least as far as development of tolerance we can be certain there are differences between these eight allergenic groups, and it may also apply to thresholds of these eight allergenic groups.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Hi, this is Eric Brittain. Back to the sample size. I guess obviously there is a concern with the 29. You are very limited in the statistical conclusions you can draw. I think the presentation that talked about the modeling may be the way to go if you are wanting to rule out very, very small rates of reactions. I don't see

any other way to allow very, very small risk.

CHAIRMAN DURST: David.

MR. ORYANG: Yes, David Oryang. Can you stay there, please?

(General laughter.)

MR. ORYANG: Yes, I'm just going to back to this just briefly. You mentioned that detection levels should be tied to threshold levels in your presentation earlier. Until the threshold levels are determined, we need to know what the detection levels are in order to determine threshold levels.

However, this analytical methods-based approach I am just wondering whether there have been any studies that have looked at the detection levels, taken the detection level, let's say, 2.5 parts per million for peanuts and then taken it, whether it is peanut butter or a whole peanut, and at that detection level maybe looked for a specific protein within the peanut that an individual reacts to?

You take that detection level and you design your study and challenge people at that

really low level and increment from that point as opposed to increment from a much, much higher level. I don't know whether there are any studies that have done that and whether there have been any results that have shown any positive results?

DR. HEFLE: There have been no studies that have started out at a detection level for a commercial study and then decided to challenge at those levels. That decision has not gone from that aspect of it.

When we sat around and thought about the consensus protocol, the levels were designed to try to incorporate what we felt were good starting levels and lower starting levels than normal.

When you calculate from those levels -- we came up with starting at 10 micrograms or starting at 100 micrograms, which 100 micrograms is kind of a magic number that has been used out there for subjective symptoms reported as causing subjective symptoms in peanut-allergic people -- when you calculate what you can detect, then 100 micrograms is appropriate in the detection limit of the

assays, around 10 parts per million or so.

Where those subjective symptom numbers lie, the test kits can easily do that level. Right now, actually they are better than that. However, no one has designed a study to actually see if the detection limits are protecting human health at this point. We think that they are lower than what they need to be, but we've never designed a study that way.

MR. ORYANG: Okay. David Oryang again. Just following up on that, I see the analytical-based approach at least beginning to set some of those lower limits. If industry has already looked at these things, there is some value in at least starting there and then adding on with some of the other methodologies the challenge test to really find out whether people react and starting to understand the dose response.

Why I'm talking about these analytical methods-based approach, I think it has implications on other allergens that have cumulative effects as an example.

DR. HEFLE: I'm sorry? Other allergens--?

MR. ORYANG: That have cumulative effects.

DR. HEFLE: I'm not as good a person to ask that question of. I guess I would point to one of the physicians.

DR. TEUBER: Suzanne Teuber here. Yes, in a situation of disorders like chronic atopic dermatitis, there may certainly be effects from small doses ingested.

(Simultaneous discussion.)

MR. ORYANG: Small doses?

DR. TEUBER: Yes, you have exacerbation. Some of the challenge studies that are in the literature, actually symptoms don't show up for three days to seven days. That is also true with some of the gastroenterological disorders, it may take a little more time.

CHAIRMAN DURST: Yes.

DR. NELSON: Mark Nelson. I just wanted to make sure we understand what we are talking about when we mention the analytical approach or the analytical method.

As I read it, it reads that we would set a threshold based on whatever we can measure in a validated way, and then next week if we can measure something 1/10th of that, then that is the new threshold. It is not necessarily connected with a reaction or a lack of reaction.

MR. ORYANG: Yes. David Oryang. Yes, that is true, and that is why I am not saying that they should be used to set the threshold levels. I'm just saying that this should be a starting point I believe that will enable more studies to be done, the challenge tests, and so forth. I think it is a good starting point, if that is the only thing that one has.

DR. NELSON: This is Mark Nelson again. That raises a question I wondered, Sue, if you could clarify. You mentioned 100 micrograms was the magic number for a challenge test, and then it was equated at 10 ppm in the test. Was that 100 micrograms of peanut, or 100 micrograms of peanut protein versus 10 micrograms of peanut, or 10 micrograms of peanut protein?

DR. HEFLE: I'm going to pass that. I'm going to pass that to Dr. Taylor.

(General laughter.)

DR. TAYLOR: When we published the "Threshold Paper One," 10 parts per million is 10 milligrams per kilogram. If we then assume that the serving size for the food is 100 grams, and we could have a whole day's debate on serving sizes for food, but if we did that, then that is one milligram.

DR. NELSON: Gotcha.

DR. TAYLOR: If we look at the clinical threshold trials that have been done, 1 milligram is in the neighborhood of where the most sensitive individuals that have been reported have the onset of these mild, objective reactions.

Therefore 100 micrograms, where the subjective reactions have started in some of these studies equates to 1 part per million, which is about the lower detection limit of some of the analytical methods.

That is why we think that the analytical

methods are pretty much in the order of magnitude of sensitivity that they need to be because of what we do know about threshold doses.

If you get below the limit of detection in one of these analytical methods, you can be reasonably certain as a food industry that you don't need to declare the presence of milk or peanut or whatever it is on the label of that product.

CHAIRMAN DURST: Doug, did you have something?

DR. HEIMBURGER: Yes. Doug Heimburger. I don't know if this will shift the discussion, it is a little bit related but not entirely. With regard to the question raised by Ms. Atagi, the first person that made public comment, urging FDA to consider sensitization as a possible endpoint of concern, how much is known about sensitization? Are there levels that can be associated with sensitization as opposed to not? This may be for Suzanne or anyone else. I don't know, maybe you can dispense with it quickly, and say we know

nothing.

(General laughter.)

DR. TEUBER: Yes, you see my smile and I'm shaking my head. Oh, gosh, there is a vacuum here. There is great concern that there is sensitization via breast milk. There is concern that in some cases because of first-exposure reactions as a neonate with first feeding that there has been sensitization in utero.

There is concern about cutaneous sensitization. This is an area of tremendous research right now of just the environmental presence of peanuts causing sensitization transcutaenously in kids who do have atopic dermatitis or some breakdown in the skin barrier.

In terms of the amount that causes that -- oh, my goodness, yes, I can say that we just are not there at all to be able to make that an endpoint.

DR. HEIMBURGER: Okay.

DR. TEUBER: It is a wonderful point that she raised, but I don't think we have the science

to be able to do that. Again, this is Suzanne Teuber.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek. Just a comment. Probably if you draw blood on all of us sitting here and do a RAST for the eight major allergens, a number of us will have, I don't know, 3 kilo units per liter to various allergens.

We eat those foods, and we are completely fine, but we are sensitized. It is very difficult. That is why the RAST is always something what has to be considered with the clinical picture.

The "sensitization," first of all, how do we define it? We define it by level of specific IgE, if we talk about immunohypersensitivity. Then, we have to go what is the level when we say that we are sensitized? Is that more than zero of the CAP/RAST that Pharmacia has, let's say. Sensitization is not really practical, I think.

DR. BOCEK: It is not practical?

DR. TAYLOR: It is not because if you define it a RAST to some extent without any

clinical histomorphology, what does it mean?

DR. HEIMBURGER: Right. Doug Heimburger again. Are you saying that because we would find that all of us had specific IgE to various ones of these allergens but we wouldn't have had any knowledge of how much exposure we'd had, therefore we wouldn't know what doses had been required or what exposure levels had been required to create the sensitization that you pick up in the RAST test?

DR. BOCEK: Petr Bocek again. Well, as far as the exposure levels, anybody with a regular diet is exposed to tons of major allergen groups.

DR. HEIMBURGER: Right. Right, so you couldn't set a threshold in that case because we have been exposed to a lot and perhaps we have developed a little bit of specific IgE.

DR. MALEKI: Again, Soheila Maleki. There are still theories out there about low-dose exposure kinds of sensitization at an early age and others say high-dose exposure is protected.

High dose frequently is protected, and low

dose at low frequency or intermittent, that is sensitization. Right now, all of this is being challenged, and it is all theory, so there is really not much speculation about determining a threshold for sensitization because we really have no idea how it happens in the first place.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek again. Just in connection to that, there were current reports by Gideon Lack's group from the Royal College for London where they looked at kids in Israel and kids in England and looked at peanut allergy.

Surprisingly, there is about more than an order of magnitude lower peanut allergy in Israel than in Europe. One of the possible reasons, which is now being intensely investigated, is the fact that Israeli children, Jewish children, have early exposure to high doses of peanut protein through a snack called Bamba, which basically since most of them starting at six months of age start sucking on it and eating it and eat basically 2 full grams of peanut protein a week.

There is certainly high-tolerance probably happening, and it is currently in a clinical trial by Gideon Lack in London looking at that.

DR. BRITTAIN: I haven't really heard anybody talk about this, but just because something is a serving size doesn't mean somebody is going to eat just one serving size. Someone might eat 20 cookies. It seems like that should be taken into account. If something is labeled essentially by the absence of saying it has peanuts in it or whatever, people may think it's safe and then they eat 10 servings worth. That should be taken into account.

CHAIRMAN DURST: David.

MR. ORYANG: Yes, David Oryang. Just going back to methodology, just briefly, the analytical methods-based approach. The issues that FDA has put before us here that need to be considered when using analytical methods-based approach.

Just touching on one of those issues, I don't know whether Dr. Taylor could comment on

this, if anything has been done, but someone had earlier brought up the issue of sensitivity and specificity of the methods and of the kits, the fact that there were varied kits and a lot of them hadn't been specifically validated. Are there any that you know the specificity of and the sensitivity? Is this standard published before you start using the kits?

DR. HEFLE: Well, these are proprietary products, but when people ask questions manufacturers are glad to provide things that aren't apparently trade secrets. They will provide manufacturers and others with information on cross-reactivity.

You can get tables from them. They have done all of this. If you ask for it, you can get the data. It is not something they put in the kit inserts that the average person pulling off the shelf can read about all of the cross-reactivity, so they test out with a matrices.

There is specificity and sensitivity known and cross-reaction amongst things, but I guess you

have to call the manufacturer and ask the questions. Some people aren't willing to do that. They expect it to be out there and everywhere. That has been one of the hurdles in getting people to just call and ask.

For most of the companies that I know of, they are willing to share this information with somebody that is truly interested and not just looking for trouble. That information should be available from the manufacturers, to my knowledge, and be available from the government, too.

MR. ORYANG: The methods have been validated by the manufacturers?

DR. HEFLE: Yes. By the manufacturers, yes.

MR. ORYANG: Okay.

DR. HEFLE: The only validation that hasn't really been done in a lot of cases is in an interlaboratory kind of trial to make sure that it performs the same way in different -- that is pretty much the way I understand the validation that needs to be done.

MR. ORYANG: I see. Is there any move to do that or--?

DR. HEFLE: There are lots of efforts going on around the world not so much at FDA right now, although I know they have been working on as best they can, given the budget that they have.

Yes, if we could get past this validation, I think everybody could be comfortable that we could use the methods for a lot of different things. It is already being used and being validated in other parts of the world. Germany has their own system.

They do their own validations. They do ring trials to get it done, and they use it. I think we just need to get some more of these international trials done. There are efforts.

Again, that takes money and time and materials and reference materials, too, which is why some of this has not been done yet. There is no funding available to do these. That is a pretty substantial amount of funding to run one of these and coordinate one of these, so that is not

inconsequential.

CHAIRMAN DURST: Pat.

DR. CALLERY: Pat Callery. To follow up on that, it looks like there will probably be some good advancements in this area. The concern about sensitivity and specificity comes in part from the comment I think I heard a few minutes ago, that in fact this test is related to peanuts rather than the allergen itself. The specificity might very well be to deal with the specific allergen.

In our writeup that we were given, in the preliminary information, there is one reference by Shefcheck that is on the confirmation of the allergenic peanut protein, Ara h 1, in a model food matrix using liquid chromatography/tandem mass spectrometry.

This is a technique that is incredibly sensitive and specific, and if they can look for the specific protein, I think that there will be great advancements. I think the method was not supported much in the writeup, because it is a potentially expensive, time-consuming method, but

it has a chance of providing the information that we are after.

DR. MALEKI: Soheila Maleki. One, manufacturers as well as consumers wouldn't really necessarily care if there was a specific allergen in there. They just want to know if that food is in there. Particularly, the different allergens and the different proteins interact with different processing in different ways.

For example, Ara h 1 becomes highly insoluble in the case of roasting. You can't test it if you are just testing for that. You have a much better chance of detecting peanut protein or something in there if you are actually targeting the peanut protein, in other words, you have much more sensitivity. You have really high specificity to detect small amounts.

Now, if you had large amounts of something else in there that it possibly would cross react with, then you would get a non-specific response. However, when you have small amounts and you are trying to detect trace amounts, in that case

cross-reactivity is very rare. I don't know if that helps.

DR. CALLERY: Pat Callery. If you are trying to set a value, it is best to look for a single entity that is not going to be changed from matrix to matrix.

DR. MALEKI: That is a good idea, but it won't work because those individual allergens will change from within one matrix to another. Like I said, you have a much better chance of detecting them, if you can detect multiple proteins rather than just one.

That way if it is there, you will always know. Even if Ara h 1 doesn't go in the solution or Ara h 2 falls out of the solution or is broken down, you still have a chance to say, yes, there is peanut there. There is less chance of error, actually. That is pretty much well known within the industry and the manufacturers.

CHAIRMAN DURST: Yes.

DR. KELLY: That brings me to another comment or question.

CHAIRMAN DURST: Name?

DR. KELLY: Ciaran Kelly.

(General laughter.)

DR. KELLY: Ciaran Kelly. That is, the issue when we are talking about validation of assays, we also need to consider standardization of assays. They are not quite the same. Someone may have done a lot of work to validate and demonstrate that their assay measures what they say their assay measures.

However, we also want to be in a world where if different assays are being used, they can be cross referenced. I think that is very important.

There are also important methodological considerations there, particularly when we are talking about polyclonal reagents. That is something that I think also needs to be addressed, because ultimately it is likely that those assays will be used to measure whatever threshold levels are being used.

CHAIRMAN DURST: Dick Durst. Along

similar lines, the matrix effect is one of the most serious problems I think with these assays. The assays in buffer solutions, and so on, can show tremendous specificity, sensitivity, and so on.

However, when you have the matrix effect, that can greatly affect the extraction of the protein that you are interested in and cause interferences, and so on. That is where a lot of the problems come in. A lot of work also has to be done in the development of protocols for extracting the active ingredient, the allergen that we are interested in.

DR. MALEKI: Soheila Maleki. Just in answer to Dr. Callery, again, to reference what you are talking about between standardizing between the kits, that has come up a lot.

It is an issue that I think is going to be addressed in developing some type of standard by maybe one manufacturer that can allow all the kit manufacturers to standardize their kits, so that later that can be related to actually what the threshold doses are, which is what they are

determining now. That is one thing.

As far as the matrix effect, there is really not a whole lot you can do with that except as technology increases. Right now, the extraction methods are getting better and better.

Better buffers are being used and better treatments, whereas you are getting a lot more consistent results between the kids and by the kids themselves. Therefore, when you do the experiments, you are getting more, essentially, consistent results, and so forth.

CHAIRMAN DURST: David first and then Ciaran.

DR. KELLY: Ciaran Kelly. This is on a different topic, so I don't know if there is another question on the same topic.

CHAIRMAN DURST: Okay. David had his hand up.

DR. KELLY: You might want to continue.

MR. ORYANG: Well, it is similar, about the sensitivity again. I just wanted to follow up with Dr. Taylor or anyone else, again, just

highlighting this analytical methods-based. What allergens have, let's say, caused a response in individuals at the levels of detectability of some of these methods? Do we have a list of that so that at least we can begin to say, okay, the analytical methods-based approach could be used on these things, because right now we know that the level of detectability is similar to--?

DR. TAYLOR: Well, when we worked to develop the detection levels of these tests, it was absolutely our goal that no patient would react at the limit of sensitivity of the test. I am actually quite hopeful that I will never find that case, because we were trying to be conservative.

If you get a negative result on this test, you are going to advise the food industry to go forth and not label this product. Why? All of these people are going to buy this product and you don't want their children to react to it. We don't know that anyone reacts to reasonable serving sizes at those levels, limits, of detection.

MR. ORYANG: Okay. The follow up, what

allergens react to, let's say, hundredfold levels, a hundred times the level of detection?

DR. TAYLOR: Again, that is kind of a hard question to answer.

(General laughter.)

DR. TAYLOR: Help me work through this analytically, 2.5 parts per million, a hundredfold higher than that, 250 parts per million. Two hundred and fifty parts per million would be 250 milligrams per kilogram, 25 milligrams.

If I looked at all of the data, and again I'm assuming a 100-gram serving size -- a heck of an assumption, but we will go with that because the math I can do in my head in the late afternoon -- if we look at all the data on all of those studies, I would say that a relatively modest percentage of the challenge patients with published data would react at 25 milligrams to peanut, milk and egg.

We have almost no data on wheat and soybean and fish and crustacean shellfish. In fact, there wouldn't be any data out there, limited as it might be, on soybean to suggest that 25

milligrams of soybeans is hazardous to anyone.

MR. ORYANG: Thank you. I just wanted to get some kind of reference point for the applicability, direct applicability, of the analytical methods-based approach.

DR. TAYLOR: Yes, I mean, I see what you're driving at. It would be my view that if you use the 2.5 part per million level as your interim threshold level, that would be a very conservative approach.

Like I said, I hope I never meet the person that would react at that level, because it was the intent for that level to be safe for virtually everyone, if not everyone.

DR. KELLY: Ciaran Kelly. Actually, Dr. Taylor, you may want to address this question also. I wanted to return to the question of the sensitivity of the challenge studies, particularly the question as regards whether symptoms or signs are used.

I am a physician also and I reiterate Marc's comment that for a physician about objective

symptoms versus subjective symptoms. It burns a hole in our --

(General laughter.)

DR. TAYLOR: I usually call them "reactions," so I guess I get away with it either way.

DR. KELLY: In any event, can you give us a sense of where the field is at present? Because the objectives may be different in terms of clearly signs are going to be much more objective and much more specific, but we perhaps would have a greater desire to have sensitivity in identifying thresholds that may cause an allergic reaction.

Are you aware of any studies that are specifically looking at that, looking, for example, at what is the difference in dose between a symptom but then goes to a sign? Is that being looked at, or has the field sort of abandoned symptoms?

DR. TAYLOR: Well, I don't know if they've abandoned, maybe neglected it. Dr. Teuber made this point earlier, and she is absolutely correct. Many of these studies that I referred to and that

Rene Crevel used in drawing his curves are actually diagnostic challenge trials.

If you are trying to diagnose a patient to determine if they actually have a given food allergy, you want to see signs. Almost all of those clinicians, I think, would proceed to actually physically observable symptoms.

However, that doesn't mean they wouldn't pay attention to subjective symptoms that might occur along the way as they are increasing the doses and the person says, "My mouth itches" or "My stomach hurts." I think you would pay attention to that because it would alert you to the fact that the guy might have a more significant event the next dose.

There have only been a limited number of studies where people have done threshold trials where they actually went through the subjective symptoms and got to the objective signs.

The study we did with Jonathan Hourihane and others on peanut thresholds published in 1997 was one of those. Admittedly, it was modest. It

was the first threshold trial that ever got done.

It was 14 subjects, 2 of them reacted with subjective symptoms at 100 micrograms. They got several doses after that, and one of those individuals first developed mild, objective signs at 2 milligrams and the other at 5.

As you wrestle with this, in my view, whether you use signs or symptoms, it is a question of how much uncertainty you assign to those numbers, how big the uncertainty factor is.

As I alluded to this morning, I would advocate using a smaller uncertainty factor if you go with subjective symptoms than you would if you went with objective signs.

Although, it is still not even that simple, because if the person had objective signs at 500 milligrams in a diagnostic trial, I am real concerned about what might happen at levels far below that.

DR. KELLY: The consensus protocol, how does that address this issue?

DR. TAYLOR: The consensus protocol that

we published last year, the consensus was to go to objective signs in these threshold trials, but to pay attention to subjective symptoms and record them, record the doses at which they occurred.

I mean, these studies cost a lot of money. I believe in capturing every conceivably significant data point, because I don't know how regulators are going to use this information, so let's give it all to them and let the wisest people decide what to do.

DR. KELLY: Ultimately, I guess that is my point, that these data, hopefully, will be gathered and it will be possible to look at subjective symptoms as a secondary endpoint and see how it relates.

DR. TAYLOR: Yes. Another point I didn't make is that I am convinced that even though clinicians have only reported LOAELs in their studies, that many of these clinicians have NOAEL data on their charts. They just haven't taken the time and effort.

In fact, I asked Dr. Sampson that question

last week and he said, "Yes, I have more than a thousand charts. If you'd like to send me some money so I can have someone sit down and look at these charts, I would be able to give you the individual NOAELs for all of the patients who did not react at the first dose. I have never published that data; I have never collated it; I've never computerized it. It is all on paper charts."

CHAIRMAN DURST: Okay. One more question from Marc, and then I would like to move on to the specific questions that FDA has asked us to address.

Marc, do you want to just finish up?

DR. SILVERSTEIN: I wanted to ask the scientific rationale for an uncertainty factor? Is it just giving you a wider range to be right about the prognostic value, that is, the likelihood that in those who are positive or negative their subsequent events, whether it be anaphylaxis or other food allergy related events?

Is the scientific rationale for uncertainty factors just being careful, or is the

scientific rationale based on what we saw earlier, intraspecies individually between species and within individual variations, or is it between symptoms and signs? What is your best judgment about the rationale by which you can provide the uncertainty factors?

DR. TAYLOR: I think uncertainty factors, the old standard -- I went to school in toxicology -- was this hundredfold uncertainty factor. It was tenfold for extrapolating from mice or rats to humans and tenfold for interindividual variations among humans. That is mostly very arbitrary. Although I was told in graduate school, and never went back to look it up, that it actually has a basis in fact.

It came about from some famous drug contamination episode called the "elixir of sulfanilamide episode," back in the 1930s, where they actually had animal data and they actually had human data from the poor, unfortunate souls that succumbed to this contaminated drug. It has some basis in fact, but it is a lot of expert judgment

not so much biologically based in some cases.

DR. SILVERSTEIN: Let me comment, then, and again highly relevant to the FDA with that historical example, this would be inferences drawn from toxicologic studies where live proportions of the population might be susceptible to some range of exposure?

In contrast, though, in allergic diseases we are dealing with not a large proportion of the population but a substantial fraction of the population that might have within individuals much more range in terms of sensitivity.

What I'm leading to is I might want to be more cautious about taking from a toxicologic exposure to an allergic disease mechanism the same range of uncertainty.

DR. TAYLOR: Yes. It is hard to address that point, because most of our experience with uncertainty factors deals with toxicologic exposures where the whole entire population is conceivably at risk. Here, admittedly, we have a smaller proportion of the population that is at

risk.

Conceptually, I don't have a problem with using uncertainty factors, because the goal is still the same: Protect a fraction of the population or protect the whole.

I think I'm bringing you back to what Rene said about using the models and then doing a better job of documenting whether the decisions that are made are appropriate by attempting to validate whether the model is correct or not.

We actually have a lot of data now accumulating very rapidly from all of these analytical determinations that are being done in industry and in academic laboratories and government laboratories about levels of allergens in products that do not have adverse reactions associated with them.

Now, you could probably get even better data if you could analyze what some of these consumers have actually eaten that did not make them sick. Based on my experience, I am almost sure that they eat tiny, tiny amounts of milk and

egg periodically, even though they don't know about it. That would help you determine whether the numbers you selected were achieving the goal you wanted to reach, and I don't know how to determine that otherwise.

DR. SILVERSTEIN: Dr. Crevel is not here. Could I follow up with one question about the modeling approach?

CHAIRMAN DURST: Okay.

DR. SILVERSTEIN: I found that modeling approach very interesting. He selected an ED10 and ED1. Is there a rationale for having the ED1, which for me would be saying we're looking to see a threshold that would affect 1 percent of the population?

DR. TAYLOR: One percent of the allergic population?

DR. SILVERSTEIN: Yes.

DR. TAYLOR: Yes. Well, the ED10, your model should predict that because if you've got 29 observations, you've got the ED10. If your model doesn't predict an ED10, it is truly a lousy model.

The ED1, I can't remember the binomial distributions, but you've got to have a lot of participants to get to the ED1, so you have to extrapolate.

I'm not much of a statistician, but you are going to get a lot more variability in guessing ED1, and you get even more variability if you tried to surmise what the ED 0.1 is.

But then if you used one of those, my argument is you could see what the experience is of the allergic individuals in the population. If you choose well, then all of the allergic individuals stay well; and, if you don't choose well, some of them are going to get sick. That is why I think it is important to follow this up and see whether we chose well enough.

CHAIRMAN DURST: Okay. Thank you very much.

I think, as I mentioned, we really do have to address some of these questions put to us by the FDA, since our time is going to be limited tomorrow. We will be focused on glutens, and then

Friday will probably be a somewhat truncated session. Hopefully, we can get through a number of these questions before 7:00 or 8:00 tonight.

(General laughter.)

CHAIRMAN DURST: I think the general questions probably can wait until we've had the gluten discussion because they probably address both aspects, but, specifically, the food allergens. Why don't we just take these questions one by one, and, hopefully, come up with some kind of conclusion or consensus for the FDA.

The first one: "Are there distinct subpopulations of highly sensitive individuals within the allergic population for each of the major food allergens?"

Would anyone like to address that?

(No verbal response.)

CHAIRMAN DURST: My goodness, what happened to that talkative group?

(General laughter.)

DR. HEIMBURGER: This is Doug Heimburger. Clinically, anecdotally, yes, people do respond,

allergic people within the subpopulation. There are subpopulations who respond both more severely and at lower levels, but it sounds like we really don't have nearly enough data to be able to say just how we identified those people; is that correct?

DR. BRITTAIN: Erica Brittain. Yes, I don't know how you would distinguish between a subpopulation versus a continuum. I mean, obviously there is variability and sensitivity, that's for sure.

DR. HEIMBURGER: Yes.

DR. BRITTAIN: Whether it is a continuum, I certainly don't know.

DR. MALEKI: Soheila Maleki. I think that Dr. Wood, who unfortunately isn't here, really addressed that question fairly well this morning, showing the range of the reactions and the populations.

However, I also think the answer to that is, yes, that there are individuals that are highly sensitive that can be set apart from the rest of

the group in some ways.

Generally, I think if we go back to that presentation that it would be very sufficient in explaining the percentages as well as the range of reactions going from IgE-mediated to gastrointestinal and other types such as celiac disease.

CHAIRMAN DURST: Does the Committee feel that this applies to each of the allergens or--?

DR. MALEKI: I think so. I mean, I think even, for example, in some cases when egg and milk are outgrown as an infant, there is a severely allergic population that will not outgrow it. There are always the exceptions or the highly allergic. Maybe Sue or one of the clinicians may be able to address that.

DR. HEIMBURGER: Doug Heimburger. The fact that they grow some of those means that they are at some points in their lives more sensitive than they are at other points in their lives. The answer is, yes, there are definitely more sensitive and less sensitive.

DR. MALEKI: Yes, I agree.

DR. KELLY: Ciaran Kelly here. Sorry to disagree and maybe pick on words, but are there distinct subpopulations? How can we identify these individuals?

If there are individuals who at one point in their life are very sensitive and later less sensitive, then to me they are not distinct; they merge one into another.

I think my clinical experience is that it is a continuum, that there is not a group of individuals who are highly sensitive, a different group who are moderately sensitive and another group who are not sensitive at all. There is a whole population. I don't think we can subdivide them into subpopulations.

DR. WASLIEN: Carol Waslien. Can you divide them on the basis of how many epitopes they are sensitive to? Some are sensitive to only one of the proteins in peanut protein, some are sensitive to two, some are sensitive to three, and some are sensitive to soybeans as well as peanuts.

There is that kind of subpopulation, and those are not on a continuum. Those are distinct characteristics. There is that kind of differentiation on the basis of some of the differences.

DR. HEIMBURGER: Doug Heimburger.

(Simultaneous discussion.)

DR. MALEKI: Soheila Maleki. Oh, I'm sorry.

I was just going to say that right now, they are doing microarray analysis on individualized epitope mapping in relation to what relationship that has to the type of reactivity that these individuals are having. They have identified specific dominant epitopes that are more likely to occur -- their IgE is more likely to recognize, if the individuals have severe reactions.

Again, going back to what you were you were saying -- and I would like to hear from the clinicians, maybe Suzanne Teuber, about the fact that, yes, there are definitely subpopulations that

are severely allergic. Does anybody else have a comment on that?

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek. Well, I think the question is posed in order to then actually follow with the uncertainty factor. It is not whether we can define this subpopulation by a specific biomarker, but it is asking whether the eight major food allergy groups, are there people with severe allergy? The answer is yes.

It is basically asking within the population of people who are allergic to these foods, what is the range, what is the factor we apply in order to be safe? I think the simple answer to the first question is yes.

DR. MALEKI: I agree.

CHAIRMAN DURST: Okay. David.

MR. ORYANG: Yes. Just following up on Dr. Bocek -- David Oryang -- I think the sensitive individuals, the allergic population, has already been divided up. The children react differently from adults to a lot of the allergens, so there is

already those subpopulations.

Beyond that, maybe there are even subpopulations within that. Right now, are the safety factors to be applied to children the same as the safety factors to be applied to adults or not? That is the question. Should they be the same? I don't know.

CHAIRMAN DURST: By the "safety factors," are you talking about these uncertainty factors?

MR. ORYANG: The uncertainty factors, right. Yes, the uncertainty factors.

DR. HEIMBURGER: Severity of response factor as well.

DR. MALEKI: Soheila Maleki here. I think that one, not all, but maybe some of the allergenic substances for adults and children will be the same. However, there are specific allergens that are adult allergens that are not child allergens, for example, egg and milk. I don't think we should consider the safety of a child more than we should consider the safety of an adult. I think life is precious.

MR. ORYANG: That's true.

DR. MALEKI: I don't think that is the term to subdivide it. If you were going to divide it into anything, it might be the different foods to consider. Even in that case, I don't think we should make that distinction. I think everybody should be protected or that's who we should consider.

MR. ORYANG: You are saying we shouldn't divide it into any subpopulations?

DR. MALEKI: Well, I think severe reaction versus non-severe reaction but not, like, separating children versus adults or men versus women, and so forth.

MR. ORYANG: That's an example. If there is a real difference in their reaction or an adult response, and so forth.

DR. MALEKI: Oh, I see.

MR. ORYANG: I mean, if there are major differences, if you can break the whole population up into different ways in which they react to the same dose, a child versus an adult, are they going

to react the same? Then, also, the exposure maybe also needs to be considered and all those things.

The safety factor I think in children's food, isn't there a much higher safety factor for some of those kinds of things than other commodities? I don't know whether some of the industry people can respond to that.

CHAIRMAN DURST: Okay. Suzanne and then Doug.

DR. TEUBER: I had a specific question. I was just going to bring up that between children and adults, for instance, most of the deaths are caused by peanuts and tree nuts and then seafood for a smaller percent, at least that is in our culture.

As time goes on, Sicherer in that Johns Hopkins group and now Mount Sinai have shown that in follow-up interviews for many of the kids who have peanut/tree nut allergies, the reactions actually became more severe with time, but we don't know what happens to the thresholds. I don't think we have that kind of age data, and I don't know if

anybody is studying that right now.

DR. HEIMBURGER: Doug Heimburger. To point back to the question again, as Petr did, the question is not asking us to identify subpopulations; the question is asking us is 10 times 10 equals 100 a sufficiently wide range. That is a different question from can we identify them.

CHAIRMAN DURST: What is the answer?

DR. MALEKI: Soheila Maleki. I just wanted to add a comment to Suzanne's comment, that they have actually identified, they have determined, that individuals between 11 and 33 are more likely to suffer anaphylaxis and have fatal anaphylaxis, because that is when they start experimenting with food. That is the age range, if that was a question. Again, the bottom line answer to this is pretty much yes.

CHAIRMAN DURST: Yes?

DR. BRITTAIN: Well, are you asking to answer the factoring question.

(General laughter.)

CHAIRMAN DURST: Yes, the statistician, please.

DR. BRITTAIN: Well, to me it feels really arbitrary. It goes back to the question I posed at the beginning of the discussion. I mean, I don't know if we are aiming at -- we want to make sure there are almost no reactions in the most sensitive population. If that is our goal, that affects how we would choose the uncertainty factor.

We would want a bigger uncertainty factor if we are really trying to focus on the supersensitive patients. If we are just trying to say something about all allergic patients, then you might not need as big an uncertainty factor.

It also depends on what data you used amongst the studies. Are you only including those studies in allergic patients? That is all part of it, too. It is sort of hard to answer this question in isolation.

CHAIRMAN DURST: She asked and answered it.

DR. BOCEK: Petr Bocek. Well, I think at

least what I'm hearing is we agree that the safety assessment-based approach is good and valid and it is fine. The concern I have, and we have already addressed that, whether the current data is targeting the right population.

At least in this country even considering the more aggressive approach in Europe, we're still certainly missing the most allergic patients because we are doing diagnostic challenges, the majority of them.

If you want to base the uncertainty factor on that, on the LOAEL determined from these studies, and you think about, let's say, 2,500 milligrams being the LOAEL in these studies -- I'm just pulling a number -- and then you have a patient, anecdotal evidence of kids anaphylaxing and adults anaphylaxing just to the peanut powder when somebody opens a bag of peanut, and there are case reports of that, that certainly is more than 100, less milligram exposure than 100 milligrams in those challenges.

I'm not sure, you may not like me, but I

think the hundredfold, if I were thinking about the current data from the current double-blind challenges, I don't think it is sufficient.

DR. BRITTAIN: Yes. Adding to that they mention there is one millionfold, the previous statistic today, one-millionfold range in sensitivity, so I don't see how the hundred address that.

CHAIRMAN DURST: Anything else on this?

DR. MALEKI: Soheila Maleki. Just to comment, yes, there is a range of one-millionfold of sensitivity. On the other hand, just like zero levels of a particular allergen in a food is virtually impossible for the industry and manufacturers, I think to set your statistics on zero tolerance, that nobody is ever going to have a reaction, is also unachievable.

You want to determine threshold levels, that means the most severe reactors, and then pick a level severalfold below that, and that might increase the safety factor.

With the knowledge and what we have today,

I don't think it is possible to say we have to pick a level of a millionfold less. I know, I understand why you're saying it, that it is probably because of the range that is different. However, if you pick the lowest level then --

DR. HEIMBURGER: Then, a hundredfold uncertainty factor applied to that, then perhaps it is sufficient.

DR. BRITTAIN: If you had the right data?

DR. HEIMBURGER: If you have the data on who is the most sensitive person and who is that at one millionth of the other person, and then you have a hundredfold uncertainty factor. The question is, Is that a sufficient uncertainty factor? It is sounding a little more sufficient, I think, if you phrase it that way.

DR. MALEKI: Soheila Maleki. Just one comment again. Being able to test these people, most of the data that has been shown or is available is based on diagnostic challenges.

The threshold studies that are actually going to be valid for the first time or some that

have been done, maybe there are two studies, this is a beginning type of study going on.

Right now, there may not be all of that data available, but I think they are going up the right track where they are picking the most severe reactors and they are treating them and waiting and recording subjective and then objective data. That is going to give us the closest we can get with the funds and opportunities and what we know available.

CHAIRMAN DURST: Suzanne.

DR. TEUBER: Again on that, I would hate to see some of the subjective symptoms thrown out of the analysis. There are going to be individual physicians who are involved in these threshold studies who are not going to go above that, at least this is what I had heard. They are going to be more comfortable if they have a reproducible, subjective symptom in stopping.

Again, if we talk about the safety assessment as it is written, it would throw out all that data and throw out these patients who may be exceedingly sensitive, and this is some of the

population that we want.

I think this just keeps coming up as a concern for the FDA in evaluating what approach is to be used and how the future data comes in to be evaluated.

CHAIRMAN DURST: Okay. Anything else?

Erica.

DR. BRITTAIN: Erica Brittain. I guess I just wanted to make a general comment about the report. The report seemed to me, if I understood it, the recommendations in the report seemed to be feeling that the modeling approach wasn't really ready for prime time, if I understood the conclusions they drew.

I guess I'm a little confused why this, which seems, you know, just like a very vague standard or just finding some uncertainty factor, why that would be preferable to the modeling, even if it hadn't been completely validated. I just wanted to make that comment.

CHAIRMAN DURST: Is there anything else on this?

(No verbal response.)

CHAIRMAN DURST: I guess we've answered it to their satisfaction.

Yes.

DR. BARACH: Jeff Barach. I have one comment to add to it. I think it is probably a little bit premature that we should start to set values for these uncertainty factors of tenfold or whatever.

We heard from Steve Taylor that he was looking at uncertainty factors of maybe one or two. I think that reflects the fact that if we go with a 10 and 10, we are using a standard approach that has been used for pesticide residues in the food system for a while, so there is some comfort level associated with that.

However, I don't think we really have the comfort level from the data and the population studies and the challenge studies to really pin down these numbers.

I would say that using uncertainty factors will be a benefit, but I don't think we are really

quite ready to even identify the magnitude of those uncertainty factors is at this point.

CHAIRMAN DURST: David.

MR. ORYANG: Yes, David Oryang. I concur with Dr. Barach in a sense, but I add that I think more work could be done to try different safety factors and apply it in the context of the model that evaluates how many people might come up with symptoms, if the safety factor was a certain value for a specific allergen, given people's reactivity.

We can begin to capture the outliers, in other words, those highly reactive people. I think there is some data which indicates the percentage of people that would probably react up to the million times more than the average person.

DR. TEUBER: There is that, that is what has been brought up.

MR. ORYANG: Okay. There is that data, so I think some modeling probably could be done to find out, to determine, how many cases would come out of setting a safety factor at a specific level, if the appropriate models were developed to do

that. That is where the risk assessment-based approach is.

I think we can begin to start doing some of that, if we put in the distributions even the safety factor, but the NOAEL could be put in as a distribution as opposed to a point value, as an example, and you can then run a model to determine how many cases there would be of reaction at a specific safety level.

I think that is the kind of thing that FDA could do to take this a little bit further as opposed to just deciding.

I mean, it is impossible to decide just like this, to say, well, is a hundredfold good enough? There has to be a basis for saying that it is good enough.

The basis might be, well, we've reduced the number of cases tenfold or reduced it a hundredfold or we've reduced the number of cases to less than one in a million, or whatever the case is, and then you can decide that you have taken it to the right level.

CHAIRMAN DURST: Okay.

DR. WASLIEN: This is Carol Waslien. Maybe because there are so many studies, it sounds like they are almost ready to be reported. Using some of the kind of data that we would need to set uncertainty factors, maybe we can say that, yes, there may very well be differences, but we can't tell what they are right now.

However, when that data becomes available, we should be able to say what they are and make those calculations for differences using subjective and objective, using prognostic information.

Therefore, we should then use the correct scientific approach to determine uncertainty factors in something besides pesticide residues that all of us are sensitive to.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: I think you would also want to think about maybe doing both approaches, both modeling and uncertainty factors, and hope to see some kind of agreement in the approaches. I want to emphasize for both you need the right data.

CHAIRMAN DURST: Jean.

MS. HALLORAN: Yes. I think very good comments have been made here about that. This type of uncertainty factor is very different from pesticides. For one thing, we are not extrapolating from rats to humans. We are working with human data to start with.

Another one we are not dealing with sort of variability from an average person. We are trying to start with the most sensitive person and set a safety factor for them.

It is a really different task, but it is also a task for which we don't have the data that you need to start with, which is the number for the most sensitive person.

Perhaps, as a principle, we could suggest to FDA something like what Steve said, which is basically: the better the data, the less of an uncertainty factor you may need; the worse the data, perhaps the bigger the uncertainty factor that should be built in.

DR. MALEKI: Soheila Maleki. I just want

to ask, I know the Food Allergy and Anaphylaxis Network has helped in a lot of research studies because they have 27,000 members of food-allergic people.

I wonder if anybody has done, or are there any studies done to divide up highly severe to moderate to low allergic individuals? It seems like that is one of the questions that David was asking.

MS. MUNOZ-FURLONG I have not done that with our membership. I'm not aware of any studies. I will tell you from the fatality registry and the fatality studies that have been published, there have been a number of people who have died who had only previously had mild reactions.

I'm not sure we are ever going to be able to put people in neat, little boxes that says, "You're a mild reactor, and you will always stay there." This seems to move and nobody can predict when or why.

CHAIRMAN DURST: Margaret.

DR. McBRIDE: Margaret McBride. As I

listen to all of this, a couple of things come to mind, and one is that we really are looking at risk. No matter how you define the range of sensitivity there is going to be an outlier or there are going to be outliers of that very sensitive end.

In a sense, that is what people have been asking, What are we aiming for? We really know that we can't set something that will be truly safe for everyone.

The other things is, if understand again, LOAELs, if we in fact we could test everyone, we would get a LOAEL and we wouldn't need any safety factor.

The safety factor is because we can't test everyone and because we are assuming that we are not testing the most sensitive individual. Does anybody want to comment on that?

I mean, what we are trying to say is easy to say. I would certainly agree that we don't have the data to set a safety factor, but remember that we are setting a safety factor because we can't

test everyone or because, understandably, the most sensitive people won't sign up for the testing.

We have a conundrum, but we still have folks who need to read labels. I mean, I'm a clinician, so it is easy for me to live with some uncertainties because I'm forced to every day when the data isn't available.

DR. BRITTAIN: Yes, this is Erica Brittain. That brings up something that I keep thinking about. There really isn't a safety threshold overall so much as each person has their own threshold.

This is a totally different way of thinking about it. However, if you could label the food by the quantity instead of saying yes/no it is above some magic line, is that a solution, that people would know their own tolerability?

DR. McBRIDE: It may change over time, you know, maybe we need to look at yearly threshold testing or something.

DR. MALEKI: Soheila Maleki. Exactly, as Anne just mentioned, you don't even know the

reactors much less the threshold levels for each person changing. You can just choose a population that you believe to be the most reactive and determine what you best can determine.

Maybe technology will improve with time, and you an do a lot better, or more people can be tested in that way. Yes, that is a nice thought, but I don't think most people know what their thresholds would be.

CHAIRMAN DURST: Okay. Shall we move on?

(No verbal response.)

CHAIRMAN DURST: As far as the second one, we touched on it a little bit the LOAELs and NOAELs: "Is the initial objective response seen in a clinical challenge study always an adverse effect that poses a risk to human health?"

DR. TEUBER: I find this question a little bit ambiguous. An objective response in one person, so, yes, that particular response in many of these studies has been an extremely severe response, but not in the studies that were designed as a true threshold study.

They are just saying clinical challenge study. Since so many of these studies were diagnostic, there were so many people who reacted on the first dose. Yes, it could be a life-threatening reaction; but in the well-performed threshold studies, the first objective reactions have not been life threatening. It could still be clinically significant. You would want to account for that with the uncertainty factor going down below that.

DR. MALEKI: Soheila Maleki. Just an addition, the dosage again that Steve also mentioned before, the dosage with a clinical challenge study is very different than the dosage that use for threshold doses. For a threshold, you are obviously trying to determine a threshold. With a clinical challenge, you want to have a clinical reaction to say, yes, this person is allergic.

Am I correct, Suzanne?

DR. TEUBER: Yes. They could have chosen lower doses to start with, but I think people are

now choosing far lower doses to start with, even in diagnostic challenges. However, there had to be something to start with in the literature, and that is what we have.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. If I were to try to operationalize a question like that for an epidemiologic study or a clinical study, the words that I would be focused on is "always" and "risk."

For me "always" might be 90 or 95 percent. An attorney might say it is 50 percent or greater. There would be some, "Well, what is always?" It would be some large number. For us in the clinical realm, we might say it is 80, 90, 95 percent.

Then, risk to human health? Well, if the outcomes of an allergic reaction could include death among the spectrum of anaphylaxis, then we might be thinking of risks that were weak risks. Low risk would be clinically important risk.

In an epidemiologic study, we might say even those variables where the risk ratio was less

than two might be important, or we may say we are going to consider large risks that might be risk ratios of four or greater.

As I try to answer some of these questions, other than an absolute no risk and never, I would try to operationalize them in terms of magnitude knowing that in the real world clinicians and policymakers have to make some decisions.

Having said that, my subjective inclination would be to say I would think that clinicians caring for patients and policymakers would make assume that if a patient reacted positively in a diagnostic challenge with objective symptoms, that patient is at risk probably to the point where they would translate it into a recommendation for patient and the family with regard to diet.

With regard to that, I would say it seems to me that it is reasonable to say, yes, objective symptoms would be tantamount to saying essentially risk would be of sufficient frequency and

sufficient magnitude to answer this question yes. That would be the way I might approach it.

CHAIRMAN DURST: Petr.

DR. BOCEK: Petr Bocek. I think the remainder of the paragraph is actually looking at the subjective response and the objective response. I understand this first question as if you do a challenge study and your stopping point would be the initial objective response, it is asking, does it always impose this risk to human health?

Well, my answer is no. Because if you do a challenge study, a clinical challenge study, and your endpoint is the first initial objective, most of the time it is not life-threatening.

The data we have, how many people actually die during the challenge study? It is usually cutaneous manifestation, hives, or something like that. To me that doesn't pose a risk to human health. That is how I understand the question.

CHAIRMAN DURST: Yes.

DR. NELSON: Mark Nelson. Yes, I was trying to understand the question as well. It

struck me as ambiguous. I guess I have a question of the clinicians. Is the objective of a clinical challenge to try to get a response to see?

As Petr said, following on the subsequent questions, I think my interpretation of the questions it that they seem to be asking us whether the clinical challenge approach is really the best way to try to set a threshold as opposed to use it as a diagnostic tool.

DR. TEUBER: Suzanne Teuber here. Again, in interpreting this question, I am trying to figure out if they mean should they be throwing out the data of people who reacted on the first dose in the diagnostic challenge studies; and, if so, we know that they really have to have a lower LOAEL level than that.

The next question is, Is it scientifically sound to use this response to determine a LOAEL? My answer to that would be no. Again, the question is ambiguous of what was intended. Again, I would throw out data on people who are first-dose responders because they really would probably react

at lower levels. Is that what it is asking?

CHAIRMAN DURST: Steve, would you be able to address that ambiguity?

DR. GENDEL: Let me get back to you on that.

CHAIRMAN DURST: I beg your pardon?

DR. GENDEL: Let me get back to you on that.

(General laughter.)

CHAIRMAN DURST: Jean.

MS. HALLORAN: Yes. My reading was that they were trying to get at how you interpret data from clinical challenges where you've got LOAELs in the absence of NOAELs. I think all of our experts have said that if you only have a LOAEL and not a NOAEL, then you don't know what the NOAEL is.

(General laughter.)

MS. HALLORAN: Then, the third question for the safety-assessment approach, Is a proposed uncertainty factor of tenfold sufficient and appropriate to use in the absence of a NOAEL?

I don't know what others think, but from

what I've heard it seems to me like the answer is not necessarily. You just can't necessarily guess, because there is no standardized procedure.

DR. HEIMBURGER: It would be much more than tenfold.

MS. HALLORAN: Yes.

DR. HEIMBURGER: The difference between the LOAEL and what you did and the NOAEL -- Doug Heimburger -- so I think the answer to that question is no.

DR. MALEKI: Soheila Maleki. I think the answer to the first three questions is no, no, no.

(General laughter.)

CHAIRMAN DURST: That was easy. I wish they were all that easy.

(General laughter.)

CHAIRMAN DURST: Margaret.

DR. McBRIDE: Margaret McBride. Just along the same lines, really the issue of the increment, even if you are doing a threshold study, is important.

CHAIRMAN DURST: Sure.

DR. McBRIDE: Probably that's something that needs some standards.

DR. MALEKI: Soheila Maleki. I think the better question would have been that instead of a clinical challenge study to ask us about a threshold dose study, and then all of these questions would be relevant. In a clinical challenge study where you usually use higher doses, and again you don't know the NOAEL, then it is not relevant to ask the question.

DR. HEIMBURGER: Doug Heimburger. The overarching thing here is, Should data from clinical challenge study be used to set these levels?

DR. MALEKI: It is no.

DR. HEIMBURGER: The overarching answer is no.

DR. MALEKI: Soheila Maleki again. If you actually change that question to what I believe might have been intended as some clinical challenges for threshold dose studies, then you can answer some of these questions or address them.

Because most of the data that is in the literature is clinical challenge studies, the question was actually intended to see if --

(Simultaneous discussion.)

DR. HEIMBURGER: Should we answer the question after changes those words and then re-answer it?

(General laughter.)

DR. MALEKI: Actually, I think they might have been to look at the literature. Since most of the literature is on clinical challenges, they wanted to know if they can use that data in order to answer these questions. It is actually an appropriate question, and the answer is again no.

DR. HEIMBURGER: No.

(General laughter.)

CHAIRMAN DURST: Yes.

DR. KELLY: Ciaran Kelly. I agree with the second two numbers, but I would like to revisit the first numbers. The question is, "Do objective responses in clinical challenge studies always have an adverse event that poses risk to human health?" I

agree absolutely with Petr, that these are not life-threatening responses.

On the other hand, are they acceptable responses? Would an individual experiencing this response at a meal consider that they'd had a healthy meal?

I think if you look at it in that way the answer would be, yes, these are significant to risk human health, if you have a broad sense of health and well-being. Although, I agree that they are not by any means a risk to life -- probably no risk to life.

DR. BOCEK: Petr Bocek. They are asking about clinical challenge, and I don't think anybody is having a happy, healthy meal doing clinical challenges.

(General laughter.)

DR. KELLY: Yes, but the question as I understand it is -- Ciaran Kelly again -- if an individual has that level of symptomatology, would that be considered an allergic reaction in everyday life? I think the answer to that is yes, I

believe.

CHAIRMAN DURST: Marc?

DR. SILVERSTEIN: Marc Silverstein. I would like to just clarify. My thinking would be that if clinicians would translate a positive response to a clinical challenge or a food challenge test into a recommendation for dietary modification, that basically is affecting the patient's care and that is affecting their health. To me that is a simple-minded but very realistic issue.

Does it mean that the patient will have a risk of dying? Yes. How big of a risk? Maybe 10 or 15 or whatever percent is graded by the risk ratio. What proportion of patients may have it? Some proportion of the population. What would you do as a clinician based on that?

If it is a sufficient threshold for clinicians to change the management, I think it would be a sufficient threshold for parents and individuals to say that would affect what they would like to see in labeling. That is why I think

I couldn't say no.

DR. TEUBER: Suzanne Teuber. This is again why I did not say no to that, either. I said yes, if you have an objective response. You have to remember there is an uncertainty factor, and I don't know the right term to apply, but that applies to that individual based on the multiple factors that have been discussed: whether their asthma is under control, time of year, time of day, circadian rhythm, other medications, exercise. I think if you have an objective response at a dose, it certainly could pose a risk in another circumstance with that same dose.

DR. GONSALVES: I think we are doing a lot of talking here, but it seems like Dr. Taylor said that he is convinced that if you go back and look at the clinical data, you could get the NOAEL response there.

It seems to me that one would want to go back and put this on a more scientific basis, once you go back and look at those data and see where you come to your NOAEL reactions.

DR. TEUBER: Suzanne Teuber here again. Again, this would be going back to clinical data that was mainly on diagnostic challenges in populations that do not reflect all of the extremely sensitive people that folks are most concerned about, whereas the threshold studies have been really trying to recruit these extremely sensitive people.

The NOAEL data that might be obtained from funding, say, the Johns Hopkins group and the Mount Sinai group to go back might not give the levels that you would get from a new prospective challenge study that is really recruiting these people.

CHAIRMAN DURST: I think we have kind of moved into the third question there with some of these comments concerning the thresholds established for the major food allergens, so I guess we will continue on along those lines.

"Is it scientifically sound to use the threshold established for a single food allergen as a threshold for all major food allergens?"

Suzanne?

DR. TEUBER: Suzanne Teuber. I would say no, because we have the examples from soy, at least from the data that we have, that the thresholds are higher. It is actually again very, very difficult to obtain people with lasting soy allergy.

CHAIRMAN DURST: Does anybody disagree or support that?

Soheila?

DR. MALEKI: Soheila Maleki. I don't know if I would say I agree or disagree, because I'm not a clinician, but I actually have a question to add to that, to anybody that can answer it.

Is there a particular food -- again, like they say, for example, peanut -- that is the most sensitizing, that if you picked that, you would pretty much cover the thresholds for the rest, Suzanne, or somebody that might want to answer that?

CHAIRMAN DURST: David?

MR. ORYANG: It would seem from the safety perspective, the public health perspective, it says

here, "In the absence of specific data," okay. Is it scientifically sound to use a threshold established for a single food allergen?

Yes, if you get the one that more people react to or react most adversely to and use that as a safety factor, you know that the other ones that people don't react as much to will be covered. Wow, I see all of these looks.

(General laughter.)

CHAIRMAN DURST: Okay. Mark?

DR. NELSON: This is Mark Nelson. I guess the concern I have is that to use a single number, one wouldn't be basing it on the science because we do have some evidence that there are different thresholds or different sensitivities for the other allergens.

Also, then, objectively from a policy standpoint, if you are going to label everything in terms of the most sensitive or the most adverse allergen, then you are going to be ending up labeling incredible parts of the food supply, which would hamper the choices of the allergic

population.

MR. ORYANG: David Oryang. I would add to that and say, yes, in the absence of specific data and if the allergen has data and it can be compared.

I mean, if you know what to apply to a specific allergen, then I think you use what is applicable because you have the data. However, if you don't have the data, and you know that people react to it, where do you set the level? Maybe you tie it to something that you believe is rather similar or more reactive, and you know that you've covered it in the absence of data.

CHAIRMAN DURST: Okay.

DR. KELLY: Ciaran Kelly. I have two difficulties with this approach. The first is exactly what Mark mentioned, and that is, that would be setting an unnecessarily low level. For example, soy would have to be reduced to the level of some far more generally allergenic compound such as tree nuts or peanuts, that's the first.

The second is there is a fallacious

assumption here that somehow you can know which is the most allergic without knowing the level, the threshold level, for each. In order to choose the most allergic, you have to know which is the most allergic.

(General laughter.)

DR. KELLY: Basically, when you work through it, you can't do it.

CHAIRMAN DURST: Marc?

DR. SILVERSTEIN: Mark Silverstein. We often use epidemiologic studies to make inferences about individuals. We may make an inference based on the prevalence in a population or the severity of a condition in a population about what that may have as an impact for individuals.

However, that usually assumes homogeneity in the population when we are going from population data to individual data; and, similarly, going from specific allergen, we are basically assuming some homogeneity in the response.

I think we have enough evidence from other areas to say that it is this homogeneity assumption

that we are uncomfortable with. I think there is reason to believe, because we have some insight into the nature of allergic responses, how variable it is across allergens and individuals, that maybe the assumptions going from allergens to rather specific allergens wouldn't be valid; and, similarly, going from population studies to individual studies might not be met.

CHAIRMAN DURST: Dick Durst. I would just like to comment that to me this approach is very arbitrary. To me it is similar to the statutory approach. It seems to be a one-size-fits-all type of approach.

I think we have probably in the literature enough data to see that is not really a realistic way of going about it. We certainly need more data to nail these thresholds down. From what's out there even now, I think it is not the best approach to use.

Marc? Oh, I'm sorry, either Marc or Mark.

DR. SILVERSTEIN: I was just going to ask, Is Catherine Copp likely be here tomorrow?

MRS. MOORE: Yes. Yes, she is here right now.

DR. SILVERSTEIN: Oh, she is? May I ask her a question. What I found was interesting was the paradigm for the statutory approach under an exemption would say "Demonstrates that ingredient 'does not cause an allergic response that poses a risk to human health.'"

I was wondering whether there is some regulatory precedence for what degree of risk, either in terms of severity or proportion of population affected that operationalizes that: no fatalities, no hospitalizations, or is just less than some amount in a population? Are there precedents? What would you use to accept a position that said that there would be no risk?

MS. COPP: Well, I think in a way Steve Gendel answered your question when it was posed in a more general way, and that is, we are asking you to give us guidance on how to, for lack of a better term, do risk assessment evaluation, lower case risk assessment.

I'm sorry, I didn't put my name on the record, Catherine Copp. It seems to be a problem with all of us this late.

(General laughter.)

MS. COPP: In terms of applying what is the statutory standard, that would involve risk management, which could involve and likely involve more factors than simply the scientific information, so that is one piece of the answer.

The other piece is in implementing this statute we would seek to implement Congress' intention. I'm not in a position -- I am not counsel to the Center anymore, I was, some of you know that. We need to think about that along with what does that statutory language mean.

There are, just as a general rule -- and we have counsel here but I don't think he is going to answer the question any more than I am -- the general tools that we use for statutory construction would be available to us. I know that is not a specific answer, but that is really because we are not there really yet.

Do you want to ask a follow-up and see if I can avoid that one, too?

(General laughter.)

DR. SILVERSTEIN: No, I would just like to reserve the right to ask a follow-up. I need time to think about this.

(General laughter.)

DR. SILVERSTEIN: I guess I will make the inference that there isn't a lot of guidance in terms of high the risk might be or the nature of that risk?

MS. COPP: To the extent that there is guidance, maybe I can answer it this way. To the extent that there is guidance, I think as a scientist you would not find it very specific. Is that a fair response?

CHAIRMAN DURST: Mark, I think you had your hand up?

DR. NELSON: I just wanted to respond to your comment, Mr. Chairman, about the arbitrariness of the statutory approach, and to some extent it is. It is based on the scientific expertise of the

U.S. Congress.

(General laughter.)

DR. NELSON: I think also as pointed out here and I think the results of the Threshold Working Group's report this would give us a starting point to deal with some of the allergens potentially as we gather information, gather more data to deal with the others. I think it is a starting point from an operational and a policy standpoint.

DR. KELLY: A related question. To my mind, the statutory approach isn't so much an approach as almost a loophole or a back door method to set a relatively arbitrary threshold.

My impression is that the intent was to say since there is no negligible allergen present in the oils and since they are widely used, that you could continue using them, not to say that the level that might be present inadvertently in some is safe.

That is another approach that hasn't been discussed, and that is to take foods which are

currently well tolerated by individuals with allergies and determine what the levels of contaminating allergens are and use that information as a mechanism to approach what are currently well-tolerated levels.

That is an approach that perhaps hasn't received sufficient consideration because that is an approach, for example, that we will be hearing about tomorrow in relationship to celiac disease. It is an approach that has been taking patients who are currently taking foods with trace levels of gluten but are doing very well clinically.

CHAIRMAN DURST: Soheila?

DR. MALEKI: Soheila Maleki. I kind of want to -- well, it maybe semi-controversial -- follow up what Marc, too, said. Yes, it may seem like a box, kind of loophole type of thing again. Actually, I posed the question originally, but I never made any comments on this.

Anne, if you have any comments on this, well, feel free to make them because I don't want to speak for the consumer.