one question, then?

(No verbal response.)

DR. SILVERSTEIN: When you selected your empirical doses of 10 milligrams and 50 milligrams, was it based on a rationale that a ratio of a 5-to-1 dose, or was it sort of a sense that this was a lower feasible dose and a higher feasible dose of interest? I mean, how did you--?

DR. FASANO: As you can imagine, if we were absolutely insane in how to design, also 6 months we discussed how much we should go. The reality was you so package data in which the vast majority of the North Europeans consumed, roughly, 150 grams of gluten-free-based grains.

If you take this European population and extrapolate to the American one, because we want to do a study as generalizable as possible, we consume in general terms more than that.

Italians, it may be that they are at the extreme of the spectrum, but definitely we want to cover as much as we could. Dr. Catassi did a study before in which he used 100 milligrams and clearly

showed the damage. Other studies were done as well that clearly showed the damage.

We designed to take two doses -- because we wished to do 10, 20, 30, 40 or 50, but that was not doable -- in which we pretty much covered the spectrum between the 20 and the 200 parts per million because the Codex Alimentarius, you heard Rhonda, is around number 7.

They have been discussing this for ages. This 220 has been on the map there for quite a while. The 50 and 10, based on a max consumption of 300 grams a day, were chosen to cover the two ends of the spectrum of the **20/200** parts per million. That was the rationale.

DR. SILVERSTEIN: I would just comment that it seems to me in looking hard for a rationale for an uncertainty factor, we don't get an uncertainty factor approach. We get a clinical approach based on the knowledge of the exposures that have caused injury.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: I guess the questions, we

are going to have a second question about an uncertainty factor for the short-term versus long-term exposure. I know we were just asked the first question, but sort of we are talking about everything all together.

For me there is still that long-term question at least from the clinical trial, which is a wonderful study, but it only goes four months. I am thinking that I don't know if cigarette smoking and lung cancer are at all analogous.

Obviously, the longer you smoke, the greater your risk is. If we were just studying smoking for four months, we might not pick anything up. That to me is my strongest concern where the uncertainty factor would come in, because clearly with respect to that study we have uncertainty about long-term exposure.

I guess what is hard for me to evaluate is the observational data that might support the validity of the result of the prospective trial. I don't really have enough details about it, and perhaps strong enough to support it, in which case

there may not be all that much uncertainty.

DR. FASANO: May I comment on that? May I?

CHAIRMAN DURST: Yes.

DR. FASANO: The three months was also not pulled out of a hat; it was part of a long discussion how we come up with the three months. You are absolutely right, if you asked me, "Are you absolutely unequivocally sure that the fellow on 10 milligrams that do not react today will not react in 10 years from now," the answer is of course not, I'm not.

Why do we choose the three months? Because if you are exposed to dangerous levels of gluten after you have been on a gluten-free diet, because your immune system is primed, 90 percent of the people will react within three months. That was the reason why we went to three months.

In other words, the vast majority of people that have been on a gluten-free diet and they are challenged because of diagnostic purposes or because of cheating or because they said "to

heck with this diet, I want to go back and enjoy myself," not only are we experienced in what you read out there, but the vast majority will react, not necessarily clinically, but they will react in some shape or form within that period.

We are sure there are people that after 10 years they still don't react. These are the extremes. Statistically, that is how we came up with this three months. Does this for sure say that in the long-run they are going to be all right --

MS. KUPPER: The American Dietetic Association --

CHAIRMAN DURST: Your name, please?

MS. KUPPER: My name is Cynthia Kupper. The American Dietetic Association is in the process of doing evidence analysis of the gluten-free diet. Two of the questions they are looking at right now are, Is the gluten-free diet useful in reversing or stopping anemia and osteoporosis?

They are really struggling with these questions right now, because a lot of the studies

come from Europe. They are actually thinking about separating the American studies from the European studies, which might help to address this question because then we are talking wheat-starch-based, gluten-free diets versus non-wheat-starch-based, gluten-free diets.

CHAIRMAN DURST: Let's see, David first.

MR. ORYANG: Yes. David Oryang. Talking about the uncertainty, you mentioned you could not be absolutely certain that the person would not react the next time after some time. There is always uncertainty. Somehow we need to keep in mind, I think, the fact that the study was done at 10 and 50.

The other thing is I were to ask suppose the study was done at five, what would the outcome have been? Could there have been reactors? If we say that, yes, there could have been reactors, then we definitely have uncertainty.

Since we do have uncertainty, then we need to put some uncertainty factors around this parameter, then the issue becomes what the

uncertainty factor should be.

I don't know whether the FDA representatives maybe can say something about this, but the whole issue of using a distribution for an uncertainty factor, would that be considered reasonable?

Maybe an expert panel could be put together just to address that issue and at least set bounds for what the uncertainty factor should be and then look at the 95 percentile value of the overall result when you divide by that uncertainty factor, to determine the threshold value.

However, this is another issue of maybe modifying the safety factor analysis methodology to incorporate elasticity into some of those parameters as opposed to just a plain value make it a distribution. That is one alternative to deal with uncertainty about uncertainty.

(General laughter.)

MRS. MOORE: Did you have a specific question that you wanted the FDA to respond to?

MR. ORYANG: Yes, whether that has been

considered, whether there is anything in the literature about that having been applied.

MRS. MOORE: Well, wait for a moment. Did I see somebody raise their--?

CHAIRMAN DURST: Yes, Margaret.

DR. McBRIDE: Margaret McBride. It seems like one of the --

CHAIRMAN DURST: Well, he is ready to speak. Sorry.

DR. McBRIDE: Sorry.

CHAIRMAN DURST: He is coming out of the huddle.

DR. GENDEL: Steve Gendel. From my consultation with the experts, I have been told that this is not necessarily a normal way that this is done, but it is certainly something that can be considered. One of the things that we are interested in hearing from the panel are suggestions about approaches such as that.

CHAIRMAN DURST: Okay.

Margaret.

DR. McBRIDE: One of the biggest

uncertainty factors is how much starch a person is going to eat. We have to rely on some kind of judgment and education from the consumer.

If we tell them how many parts per million or set a level that is a certain amount of parts per million, then how many pieces of bread with the alternative flour they eat affects much more than any, or possibly significantly more at least equally with any uncertainty factor we try to put into deciding a parts per million.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. It seems to me that we have lots of precedents in clinical medicine where we studied either the effect of large doses for shorter duration, or we set practical limits to the amount of resources that can be placed in doing studies, and we make decisions about medications and treatments based on courses of therapy.

There might be one month, three months, six months, to a year, yet many of these conditions and exposures that patients will get, either their

treatments or medications or tests or radiation or diet, are lifelong.

With regard to the issue of going from short-term to long-term, short-term exposures and effects to long-term outcomes, I think we should be cognizant of, be aware of the fact that these are individuals with a clinical condition, with a disease, that have access to healthcare.

These individuals with the advice of their physician are going to have a course of therapy that could be periodic assessment of their response to therapy, periodic assessment of their mucosa, periodic assessment for the consequences of long-term inflammatory disease.

I am less worried about the problem of making inferences on long-term outcomes because, by and large, these are patients with a clinical condition who are having a dietary regimen under the management of a physician.

It may be unfortunate that some patient's experience has been, the physician has said, "Well, now you should change your diet. Goodbye and good

luck." However, I think we should remember that is not, indeed, the norm and probably is more the exception I would hope.

In any case, I would think that we would be able to make reasonable inferences based on the short-term exposure, and three months seems to me to be right now probably the upper limit of what was feasible in a well-designed clinical study for response to gluten.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: I guess my question about that would be I assume these patients don't get routine biopsies or anything like that, or maybe they do? Maybe that is my question. Without that, I don't know how you would necessarily know if they are doing badly.

DR. SILVERSTEIN: That is what medicine and clinical research is all about. The physicians -- those under their care, the patients -- will come up with a course of therapy.

I am sure there are physicians based on current and evolving data who will recommend either

no further surveillance or periodic surveillance or surveillance at yearly or three yearly or monthly or whatever it may be.

In the same way, for example, patients with ulcerative colitis who have longstanding disease and are at increased risk of colorectal cancer are often in a periodic surveillance program for that outcome. That would be separate from saying how we should make recommendations about pharmacotherapy for their disease.

Some people would say, okay, study a reasonable period of time -- whether it is one month, three months, or a year -- and let the patients and the physicians together make their best recommendations about long-term management.

I am just addressing this issue of short-term and long-term. Clearly, you can't wait 20 years before you make any recommendations, and experience will evolve as patients and physicians together learn more about what works and what doesn't work.

I do believe that we have many precedents

where we do have reasonable time periods -- whether it is one month, three months or six months -- for clinical studies and then make recommendations that patients and their physicians can look at the long-term outcome.

I guess I am repeating myself. However, I do feel that there is a scientific basis and precedence in many other areas for best information for a short- or moderate-term studies to be the basis of practice over the long-term.

CHAIRMAN DURST: Okay. Thank you.

Mark.

DR. NELSON: Mark Nelson. I don't know how we want to factor in the natural experiment, if you will, of labeling gluten-free products in Italy. While it is not as elegant and as controlled as the Italian study that we heard about today, my understanding is we have seven years of this labeling in Italy. We must have some real-world experience about severity of symptoms, change in symptoms, and change in prevalence in Italy with that experience.

CHAIRMAN DURST: Dick Durst. I would just like to make one comment on the uncertainty factor, that is, we can certainly recommend that there has to be a certain degree of uncertainty factors associated with the recommendation, but it sounds like from what I've been hearing that even a tenfold uncertainty factor would be beyond what the analytical methods can currently do. Therefore, it is a luxury that we may not have the option at the present time of setting.

Certainly technology in the future is, hopefully, going to improve the point where we can get down to a tenfold uncertainty below, say, that 20-part-per-million level.

DR. HEIMBURGER: Doug Heimburger. Related to that, though, but the other problem is the impossibility of creating products that are significantly below that 20, even if you could detect it. I'm not sure that new technologies will necessarily change the true uncertainty factor with regard to what is actually included.

CHAIRMAN DURST: Unless the processing

technology also improves.

(General laughter.)

DR. BRITTAIN: It sounds like maybe 10, I mean, I don't know if I was hearing correctly, from a practical point of view something like that might be the absolute lowest you could go and still be able to produce food. I don't know if that's right.

DR. HEIMBURGER: Doug Heimburger again. From what Steve Taylor was telling us it is not just a matter of farming technologies, either. You would have to revolutionize the entire agricultural methods that are used.

CHAIRMAN DURST: The infrastructure.

DR. HEIMBURGER: That is just not going to happen, particularly because they are built on efficiency now probably being as efficient and cost-effective as possible. Any move in the other direction would have all kinds of forces against it, including our pocketbooks.

CHAIRMAN DURST: Jeff.

DR. BARACH: Yes, Jeff Barach. I think

what we are really talking about here is risk management and uncertainty factors, adding uncertainty factors is one approach.

Another approach that we favor is really to establish when the threshold is established, to consider it as sort of an interim threshold, and then with experience and more information perhaps that interim threshold would change.

For us to assign uncertainty factors based on numerical and environmental considerations at this point does seem premature. With experience and setting an interim threshold, we would have the opportunity at some time to make an adjustment in that, if we felt it was either too high or too low.

DR. KELLY: Ciaran Kelly. I wanted to return to the question of timing and whether or not three months is adequate to demonstrate a response to gluten -- of course the longer, the better.

In reality, if you look at acute gluten reactions, clinical symptoms, reproducible symptoms, they tend to occur within a few hours. If you look at the acute challenge studies,

morphology could be demonstrated to be abnormal within hours of instilling toxic peptides into the duodenum. Those very acute studies were able to show abnormalities within a very short period of time.

It would seem to me that understanding that this response appears to occur within hours in vivo, having individuals exposed for three months it would seem to me to be more than adequate to demonstrate any at least medium-term effects.

There is nothing, to my knowledge, to suggest that an individual should be triggered to respond at a later period in time who hadn't responded earlier, albeit the fact that there are always exceptions to that.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: So are you saying that someone, say, who is not very compliant and does eat a lot of gluten, he would not get worse over time if he had more exposure to gluten?

DR. KELLY: Yes, he would. I mean, if somebody has severe celiac disease and they are not

diagnosed or don't go on a gluten-free diet, they can become malnourished. Before a gluten-free diet was available, the condition was often fatal. Yes, it can accumulate.

What I'm saying is that in an individual who is on a gluten-free diet and well treated, the response to inadvertent and purposeful gluten intake, if there is a reproducible, reliable clinical response, it is very rapid.

In those individuals who respond in a particular way, the response is quite rapid. As we heard, it is a delayed Type 4 reaction that occurs within a few hours of exposure, typically.

CHAIRMAN DURST: David and then Soheila.

MR. ORYANG: Yes. David Oryang. Yes, I think in an individual we can say that we expect pretty much the same thing. What about between individuals? Are we going to expect the same thing between individuals?

The safety factor that we are talking about, the intraspecies safety factor, is looking at, okay, how will he respond versus this person to

the same challenge. Can we say with a hundred percent certainty -- in other words, a safety factor of one -- that they are going to respond the same?

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. One thing in answer to yours, they are talking about being on a gluten diet and they are talking about a certain limit, not sitting around and eating a bunch of known gluten. The study is about getting a limited amount. It is showing within 45 people -- I think that was the study group, right?

CHAIRMAN DURST: Thirty-nine.

DR. MALEKI: Oh. I'm sorry?

THE COMMITTEE: Thirty-nine.

CHAIRMAN DURST: It was 39.

DR. MALEKI: Thirty-nine people, close enough. Anyway, within 39 people that they tested with this particular limit over 3 months, given that they would have a severe reaction and it would show within 3 months, that they didn't. Just clarifying that, because you were saying if they

eat a lot of gluten.

DR. BRITTAIN: Oh, no, what I'm getting at is what is the effect of cumulative exposure. Just like smoking cigarettes for many, many years, you're not going to get immediate damage from smoking -- you may get slight damage, but it might not be incurable.

I can just quickly describe a study design you might do. I know it would be hard to do, but perhaps a study for a year and do biopsies every four months or every six months, so that you could see if there is a change over time.

If the change happens right away and it doesn't go down any further, then you know, you have some confidence that there is not going to be a continued change over time, but if you see a time relationship, then you would know.

DR. FASANO: Can I make a comment on that? May I, Mr. Chairman?

CHAIRMAN DURST: Yes.

DR. FASANO: Okay. Alessio Fasano here. The parallel between smoking and celiac disease I

don't think that is really pertinent, because celiac disease is an autoimmune disease. It is a step-by-step process. The variability is how long it takes for Individual A versus Individual B to go from point 1 to point 2.

The steps are well-known. You are exposed to gluten, antigen presented in cells, and we see them represented in intraepithelial lymphocytes, there will be inflammation, cytokine production, intracellular cells, and the damage.

People can do this journey in a few hours; people can do the journey in a few days; people can do the journey in a few months. The question is, When do the vast majority of people go from point 1 to point 2? That is what I was alluding to.

When people genetically predisposed to celiac disease are exposed to gluten because challenged, a toxic amount of gluten, or challenged because they decide to abandon the diet, the vast majority of the people, they react within that time limit. When I say "the vast majority," it is because again there is still the possibility and

there are reports that you can take much longer.

It is the same story on clinical grounds. There are people that are exposed to gluten and they develop symptoms as kids after a few months or a few weeks because and then the damage will become clinically apparent in the next few weeks, but there are people that it would take nine years.

How do you explain the variability? We don't know. The first steps in the process of damage to the intestines are at the very beginning and this is likely to switch on and off. It goes on and it goes on.

That is the reason why I am pretty comfortable with the three-month business, because it is a very comfortable interval in which you should see the immune system react with parameters that can be biologically looked at as we did with histology and morphology.

CHAIRMAN DURST: Dick Durst. I would just like to say that, presumably, the whole point of a threshold amount of the gluten or whatever the problem is, is that it is a level below which the

disease has not progressed. It doesn't get any worse.

Using, even though it is a bad analogy, the cigarette, if you can show that, okay, smoking one cigarette a day is not hazardous, but smoking a pack over time will really cause serious problems, lung cancer or what have you, then the threshold is that one cigarette a day.

Presumably, if you have done good studies, it would show that, all right, that's safe to do. However, I think if we set a threshold at a point where the disease does not progress, even on a short-term basis, then over the long term that should still hold.

Marc.

DR. SILVERSTEIN: I think this is an insightful discussion because I think we are talking about immune-mediated injury, IgE, in the case of the allergic diseases or cell-mediated for celiac disease.

We are talking about carcinogenesis on perhaps a multistage process with genetic mutations

due to a variety of exposures, or we may be talking about toxicologic injuries due to environmental factors.

I think we've got a conceptual model, certainly based on environmental toxins, that we are extrapolating to these immune-mediated processes. I am cautious about that. Because I can't see that rationale coming from science, in terms of the application of the risk management for environmental exposures, toxins, being applied to these immune-mediated conditions. That is why I'm being fairly skeptical here.

The discussion has helped me think about what are the underlying mechanisms in immune-mediated carcinogenesis with damage to cell growth or other toxic mechanisms due to the environmental accumulation of small molecules.

CHAIRMAN DURST: Soheila and then Suzanne.

DR. MALEKI: Soheila Maleki. Bottom line, I think that we can talk about this, and all the complications which of course exist such as they do in the case of IgE-mediated allergy, but bottom

line based on the best data available, we have to accept this as what we know.

This is the level within the three-month study that has been done prospectively and the retrospective study that they have actually determined maybe seemingly short-term, but clinically relevant according to Ciaran.

Of course, then, we have the limitation of the methodological methods available to us. We can discuss this for a long time and not really be able to still answer that question as far as what fold we would put that at.

I mean, I agree with you that it is very complex and a multihit type of disease much the same as cancer would be. With the data available -- and, I mean, think it is good data -- that has shown that these are some of the limits they react.

CHAIRMAN DURST: Suzanne and then Margaret.

DR. TEUBER: Suzanne Teuber. It seems to me that with the population data that Dr. Collin presented you actually have a higher level already

seen in the population with some long-term data that was very reassuring.

It seems that if you use that as your starting point, then apply an uncertainty factor that we don't really know to that, and then your data comes in from Italy that is very reassuring, that a factor that has been theoretically applied to that upper limit is coming down even lower over a three-month period with no immunologic reaction seen, that is very, very reassuring.

I think that would imply that the levels that should be looked at initially would be what Dr. Collin was discussing with this additional safety.

DR. COLLIN: May I have a comment?

CHAIRMAN DURST: Oh, okay.

DR. COLLIN: Pekka Collin. Another issue is that, if one stay on the safe side, if there is somebody very sensitive, some celiacs who are very sensitive, they might react after three months; so, the period would be too short.

All our retrospective studies show that

ultimately we can achieve a complete response. We have methods to detect those patients who might be very, very sensitive.

One mechanism is that we take usually, at least in Europe or maybe also in the United States, take one biopsy after one year of a gluten-free diet.

If there is no clear improvement, then we can concentrate on those patients who might be truly sensitive, or, as I said, who might take some extra gluten, excess gluten not PPMs but grams of gluten.

Therefore, I think that it is very high, that uncertainty factor. Maybe it is not very relevant. Maybe you go to the conclusion of zero level instead of a little bit higher level, which is very well tolerated by the vast majority of celiac disease patients.

CHAIRMAN DURST: Finally, Margaret?

DR. McBRIDE: Margaret McBride. I think in a certain way that the data that we heard this morning from both studies included some long-term

data. We know what the biopsy results were in folks who had adhered to a diet, a gluten-free diet, in both countries.

In one country, for seven years "gluten-free" meant below 20 parts per million, and we assumed that they were eating somewhere between 100 and 200 or, for real past lovers, 250 or whatever.

We can calculate the amount of the number of milligrams of gluten to which they may have been exposed over a seven-year period. In fact, their biopsies were like those of normal folks, at least in regard to the height/crypt depth ratio.

Likewise, in Finland we have the same kind of data. In other words, we almost really have a NOAEL from both studies that is a long-term NOAEL. In Finland, I think Peter and I, too, was under the impression that there was a set limit, but, in fact, I believe that is not true, that the limit is in fact the current international group limit.

In fact, when the gluten-free foods were tested, all but two were below the 100 part per

million; but if you look at that slide, a good many of them were down closer to the 20 part per million.

We have data without any uncertainty factor really needed that suggests that if you adhere to a gluten-free diet in those situations, that you do quite well.

CHAIRMAN DURST: Okay. May I suggest we move on to number three?

Do you have another--?

DR. WASLIEN: Well, no, this is still part of this. I hope that we are counting as celiac disease only people who have shown clinical symptoms, right? We are not counting silent? Because if you count silent gluten sensitivity, you've got a much, much higher level of gluten that is still acceptable, right?

DR. MALEKI: Soheila Maleki. Well, if it's silent, then they are not avoiding gluten.

DR. WASLIEN: No.

DR. MALEKI: They aren't eating gluten-free.

DR. WASLIEN: It said two separate groups of patients, and I know we talked about the range of latent to silent to acute cases. The range of acceptable intake between acute cases or ongoing cases and latent is very large. I don't think we count that in the disease.

If we count only those who have "symptoms" of celiac disease, we do have this 100 parts per million, it looks like, level. If we are talking about the silent, we are talking about any level; or the latent level, we're talking about any level because they haven't shown any symptoms yet.

I think it goes back to this. Yes, we said yes, there were differences in the patient groups. We need to go back and say yes, there are differences in the patient group, and this is the group we are looking at, the ones who have acute conditions.

CHAIRMAN DURST: Ciaran.

DR. KELLY: Ciaran Kelly. To respond to that, there is a lot of debate as regards whether some, many or all individuals with silent celiac

disease should be or should not be on a gluten-free diet. I think that is far beyond what we are going to decide.

I think what I would suggest we should think of this as in those individuals who decide to go on to a gluten-free diet, whether they be silent celiac disease or be individuals with severe malabsorption, regardless of that, in those individuals who decide to go on a gluten-free diet, what appears to be a safe ingestion of gluten for them.

CHAIRMAN DURST: David.

MR. ORYANG: Yes. Just going back to the safety factor, assuming a safety factor of one, it would indicate that we have a hundred percent confidence that the parts per million, the 20 parts per million, as an example, is an absolute value below which we don't believe people would react, or no one faced with a challenge below that would ever come up with celiac disease.

I don't think that we can put ourselves in a position to say that; there is uncertainty. We

do need to look at it scientifically and be able to communicate our uncertainty to people when we do these kinds of assessments.

The way that you do that is through something like a safety factor. This specific approach uses the safety factor to communicate the degree of uncertainty we have, in other words, to ensure that we say, "Well, maybe they could react at five times less of a dose." Or, "Maybe that is the reasonable dose we believe that 95 percent of the people will react at."

Somehow we need to be able to communicate that as opposed to just saying, "Well, this is the value." I think somehow it needs to be communicated and transparent. Otherwise, I wouldn't have confidence in it if someone just told me, "Well, 10 is it." I think it really does need to be considered. We can keep talking about it later.

The approach is basically so that people can have confidence in the fact that we have clearly evaluated the data, and based on our evaluation this is the degree of certainty we have

or the degree of confidence we have in the clinical studies that were done. I think it does need to be considered.

CHAIRMAN DURST: Dick Durst. I agree that we can't be absolutely certain of the level and there has to be some uncertainty associated with it in the same way that we can't give a number for a threshold, that is not our job here.

MR. ORYANG: That is what I thought.

CHAIRMAN DURST: We are looking at the approaches. I think our suggestion to the FDA is that they do attach some kind of uncertainty factor, but that is something that, again, requires more study to find out what level it really needs to be.

Marc.

DR. SILVERSTEIN: Marc Silverstein. It seems to me that if you have observational data or you have clinical data from a randomized trial you will have number of patients per person years of observation and observational studies, or if you have two different doses, you will have risk

ratios.

Obviously, in clinical trials you have a metric, and so it seems to me that rather than saying whatever we do in looking at the literature we pull out a number, the number is going to come from a clinical study.

There will be data available in the study, either presented by the primary authors or maybe original data may be available in addition from the office -- and a statistician or an epidemiologist can look at the reported data and then calculate confidence intervals around the various metrics in the data.

It seems to me that it is not -- yes, there are reports of values, but we are not just saying, "Oh, we take 20 and that's it." You walk away, and there is no uncertainty.

Of course, there is uncertainty, but it is retrievable, either the reexamination of the original data from the author in the publication or by a review of the data. It could be that these data have some inherent uncertainty, as most rates

or rate ratios or effect differences or risk differences do.

I am not worried about getting some estimate, because I believe that we will be able to derive confidence intervals or measures of uncertainty from whatever studies that these thresholds come from.

CHAIRMAN DURST: Yes. I would like to move on now to number three, so that we can finish up at a reasonable time. This has to do with the susceptibility to oats. I guess we heard that it is pretty inconclusive at this point.

Most of the studies indicate that there is no problem with oats, whereas there were couple of studies they were. From the question here, if there is no certainty as far as the susceptibility to oats, what additional data is needed to draw such a conclusion?

Would someone like to--?

DR. MALEKI: I'll start.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. Again, the

majority of the studies by far have shown that there is no cross reactivity with oats. However, there have been some individuals that have felt like they had reactions to oats, and documented.

Bottom line, and according to what Dr. Taylor was talking about, that if they are severely sensitive and there is contamination in the product that comes from the far, then they could have had wheat exposure with an oat contaminant, otherwise oat exposure with a slight wheat contaminant that could have seemed like an oat exposure, or they could have had a real reaction to the oats. Either way you look at it, I think it is going to be hard to determine until there is more data.

Thank you.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: I don't know the original literature, but if these studies are a series of observational studies or case control studies or cohort studies, there are meta-analytic techniques for looking for heterogeneity and

homogeneity in published studies, and then if there is homogeneity, making overall assessment so you have an increased ability to make inferences based on multiple published studies.

It seems to me that this would be a wonderful area. Maybe there is a published meta-analysis of these exposures; but, if not, it seems to me that the recommendation of the type of data that could be helpful might be a well-constructed meta-analysis of the published data for the oat exposed. If we are thinking about it today, I'm sure there is somebody already working on it; and if not, somebody should be.

CHAIRMAN DURST: Okay. Anything else on that one?

DR. KELLY: Ciaran Kelly. Well, just a comment, and that is that the prospective, published studies are all in agreement regarding safety. The other studies that suggest that there are maybe a small proportion who are sensitive, essentially these case series studies are in very limited groups of patients.

Basically, those individuals appear to be outliers, and so it is not going to be possible to devise a study, a prospective study, to identify the very few patients who appear to be sensitive to oats.

The problem is you can't just make a blanket statement, "Nobody is sensitive to oats." It is unfortunate, but it does appear that there may be a small number of people.

DR. SILVERSTEIN: No, I fully understand. What I'm suggesting is if you've got 10 studies that show there is, essentially, no numerator events, you are going to have a more precise estimate about how close to zero the observed data is when you do your meta-analysis and you appropriately weight the estimate of zero and a confidence interval around it by the sum total of patients in all of the studies.

CHAIRMAN DURST: Dick Durst. While it is inconclusive, should the FDA err on the side of caution and include oats, then, or is the preponderance of the evidence against oats

sufficient?

Mark.

DR. NELSON: Yes. Marc Nelson. Basically, you asked the question I was going to ask, which is considering that these individuals seem to be very few and far between, should oats be included, and does that limit further the broader number of celiac patients enjoying other products?

As I understood it, these individuals if they in fact were sensitive to oats, they would obviously demonstrate symptoms, and then, as our clinician colleagues mentioned, they would further work with that patient to determine what the cause actually was.

CHAIRMAN DURST: Jeff.

DR. BARACH: Jeff Barach. I think if we go back to where we started with FALCPA and our charge here of looking at major food allergens, what we have found here is a subpopulation of people who are allergic, to celiac disease. That doesn't really fall under my thought about a major food allergen. It is kind of a sideline issue that

maybe is interesting and important but not for this group.

DR. KELLY: Ciaran Kelly. I wanted to say something similar in a different way, and that is, that the number of individuals who may be have an immunologic reaction to oats to cause disease is tiny.

A much larger issue is contamination of oats by grains and proteins that are known to be toxic. I think we shouldn't focus on a very, very small subpopulation and forget the big picture.

DR. COLLIN: May I comment?

CHAIRMAN DURST: Okay.

DR. COLLIN: As to the studies in the oats business, as you mentioned, there are several studies and they almost all are randomized. There are some studies which are five-year studies. That was a continuum for randomized studies.

However, there are also some studies where in Sweden they advised the patient to take 100 grams of oats per day. I can assure you that is a huge amount. It was a study by Strsrud, and they

succeeded. I don't remember whether it was half a year or one year. They did not see any adverse effects, even when the patients took five times more than our patients are willing to take.

As I mentioned, they took 20 grams, but in Sweden they tested in a randomized manner with 100 grams. It seems that pure oats is very, very safe. Of course, contamination is a problem. It is also a problem in corn and rice. If we are talking about contaminated foods to celiac people, then we are talking about wheat, not about oats.

However, there is that small study by Lundin. I would actually ask, Don Kasarda, as you mentioned oats -- wheat has been studied most thoroughly of all -- and celiacs, would it be possible that also some people who eat corn or rice would have similar reactions as those three patients? What is your guess?

My name is Pekka Collin. Sorry I didn't mention that.

DR. KASARDA: Don Kasarda here. I think that is an excellent question, and one that I've

thought about a lot. We just don't have the information. It might turn out that if you studied corn that you would find, because there are many celiac patients who say I can't eat corn, the same thing as Knut Lundin with oats.

I would like to just make one comment on something that Ciaran Kelly mentioned. Yes, contamination is a big problem, but we could possibly remove the avenin fraction, which only makes up about 10 percent of the proteins, with RNA interference.

We could possibly silence 90 to 95 percent of the avenin genes or the expression of the avenin genes to get rid of the avenin fraction. This way at least, I mean, you still have to deal with the contamination problem, but that is dealable with in my mind.

However, if you don't deal with the avenin question, if you accept the Oslo results, there is always the question, "Well, will I react to oats or not?" I think it would be a good thing to do, but we don't have any money.

(General laughter.)

DR. BRILEY: Margaret Briley. I think it is kind of interesting when we start talking about contamination. When you have to think about going back to the farm, wheat in most part of the United States is not really grown on the same land, generally, as corn and rice is not there, so the contaminations are going to have to be at the silos and at the mill area. It might be that would be an easy way to solve it, other than having to do an expensive kind of study.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Soheila Maleki. One comment to Margaret is that I virtually like impossible, especially at the silo level.

The comment I wanted to make is that we have to keep in mind here that these are maybe three or four patients and outliers. We can't forget that we are looking here at what is best for the general and the majority of the population and don't revert to going into two or three outliers, even though they might have been true cases. That

is something that I don't think we are charged with looking at as Dick Durst commented.

CHAIRMAN DURST: All right. Let's move on again to conserve time here. The next question, number four, has to do with the risk of developing consequences such as cancer and increased mortality. Would anyone like to address that one? You're shaking your heads no.

(No verbal response.)

CHAIRMAN DURST: Okay. Let's skip that question.

(General laughter.)

DR. BRITTAIN: We haven't heard any data on this, have we?

DR. MALEKI: Exactly. Soheila Maleki. As far as I know just physicians, and some of these physicians like Dr. Kelly can comment, I know they see patients that have complications as we all heard based on the talks they gave today that, yes, they can lead to cancers, they can lead to other complications and mortality and morbidity in a lot of different cases. Yes, clearly I would say the

answer is yes, because of clinical observations.

DR. BRITTAIN: Yes, that there are equally at risk?

(Simultaneous discussion.)

DR. MALEKI: I don't think they are all equally at risk.

DR. BRITTAIN: Then the answer is no.

(General laughter.)

DR. MALEKI: I mean, yes, that they are actually these cases that are seen. Are they all equally at risk? No. Clearly, if you can put them on a gluten-free diet or an appropriate diet, then they don't see as many of these risks. Like I said, the clinicians can comment more about the percentages and the people that they see.

DR. FASANO: May I?

CHAIRMAN DURST: Okay.

DR. FASANO: Alessio Fasano here. I think that the way that the question is posed is kind of deceptive. Focusing on the mortality part, yes, we know that the mortality is twice as much in the general population in untreated celiac. The

general population is not going to go on a gluten-free diet.

I don't think this issue is as much the mortality as the morbidity. For the mortality, of course the answer is no, not everybody is at the same risk.

However, if you talk about morbidity, that also equals quality of life, I also believe that it will be undisputable to everybody that not only do science with celiac disease but see patients, the answer is undisputably yes.

I mean, these people will pay a price. We are talking about the symptomatic. Otherwise, why do they come to you? There is definitely increased morbidity.

This morbidity can be reversed if, for example, we are talking about anemia. It may not be reverted if you are talking about short stature and you missed the diagnosis, because that person remains short for his or her life. That is undisputable.

I believe, again, this question should be

rephrased a little bit. Mortality? No, not everybody is at the same risk maybe. The morbidity? Definitely, everybody is at risk. Morbidity depends on from individual to individual. That is the way that I see it.

CHAIRMAN DURST: Pekka.

DR. COLLIN: I a little bit disagree with you that the mortality is twofold in celiac disease. We have to remember the iceberg phenomenon. It was in 1950 or 1967 it was told that 15 percent of patients with celiac disease eventually developed lymphoma. Now we know that it is 1 or 2 percent.

Still, we do not detect all patients with celiac disease. I think in terms of mortality and also in terms of morbidity there is a clear bias to the most severe cases. Now, what is in clinical practice? Only the most severe cases will be detected.

Pekka Collin it was.

CHAIRMAN DURST: Marc.

DR. SILVERSTEIN: Marc Silverstein. If I

were going to make estimates or inferences about subpopulations at risk, I would want to see a long-term, cohort study in which I had strata of exposures, knowing full well there is always some misclassification in epidemiologic data, but then want to know for each strata of exposure what was an element of the relative risk of an outcome whether it was death or some long-term complications.

While I certainly believe clinically these risks are not uniformly distributed across people, but when you make inferences about subpopulations, you have to be able to characterize your populations.

You could characterize your populations based on serology, you could base it on extent of involvement in inflammation in the small bowel. You could base it on other characteristics of the patient, whether it was age or gender, duration of clinical symptoms, whether you had specific markers of genetic exposure -- a whole variety of types of putative potential variables you might look at.

Unless a clinical study, a cohort study, then shows me the risk and how the exposure groups are characterized and what those risk ratios are, I wouldn't have a basis to say that the risks are unequal, although we all believe in the real world, as we get more information, the risks are unequal.

I haven't heard yet any particular markers, even gender-specific subpopulations, of celiac disease patients who would be at increased risk. Although I certainly believe there may yet be discoverable subpopulations, I don't know that there are any that we've heard about.

MRS. MOORE: In the interest of time and for our code of conduct, we are going to have to ask the guest speakers to only speak when they have been given a question.

CHAIRMAN DURST: Erica.

DR. BRITTAIN: Yes, I guess I certainly agree with what you just said. I guess I am wondering what the rationale -- how does it relate to the threshold question? Do you think the idea is that if there were individuals at increased

risk, they might want to have a separate, a different threshold, or you they might want to base your threshold on those individuals? Is that the motivation for the question? Otherwise, I am not quite sure why we are addressing it.

CHAIRMAN DURST: Steve, can you address that?

DR. GENDEL: [No microphone.] I don't think it is necessary at this time.

CHAIRMAN DURST: Okay.

DR. BRITTAIN: He doesn't feel it is necessary to.

CHAIRMAN DURST: Yes, he is probably right, we're not dealing with thresholds.

Do you want to--?

DR. KELLY: Yes, just a comment. Ciaran Kelly. I would agree. To sort of bring it together, what I would say is clearly individuals with celiac disease have different outcomes. However, we don't have information as to what specifically determines that. As far as we are concerned, from a practical perspective, the answer

is yes, as far as we know all individuals are at equal risk, insofar as we can't identify individuals at greater or lesser risk. Therefore, when it comes to terms of management, we give all of the individuals the same advice.

DR. HEIMBURGER: Right. Doug Heimburger. If we interpret the question to mean, Is there a subpopulation that is at lesser risk or at lower risk? We don't know that there is, so we need to proceed, assuming that all patients with celiac disease are at higher risk and none lower than any other from any data that we have.

CHAIRMAN DURST: Good. All right, let's move on to number five. "Is evidence of minimal intestinal pathological change -- following a gluten challenge, an appropriate symptom upon which to base a LOAEL for long-term consequences?" Are there other biomarkers that would be more accurate predictors?

DR. HEIMBURGER: Doug Heimburger. The clinicians here are all unanimous in saying that the word "symptom" in there should be changed to

"signs."

(General laughter.)

DR. HEIMBURGER: It has to be changed before we can even discuss the relevance.

(General laughter.)

CHAIRMAN DURST: Consider it done.

DR. HEIMBURGER: Okay. Consider that done.

CHAIRMAN DURST: That was your comment?

DR. HEIMBURGER: No.

(General laughter.)

DR. HEIMBURGER: What was the term Ciaran used yesterday? It burns a hole. There was a hole burned in my mind, and that has to be patched.

CHAIRMAN DURST: Ciaran.

DR. KELLY: I think that in terms of a sensitive marker of celiac disease activity and the most widely accepted marker of celiac disease activity is probably histologic change. It goes back to the definition of celiac disease, which "celiac disease" is immune-mediated enteritis.

The presence of intestinal inflammation

and the consequences of inflammation, which are the architectural changes that you see in celiac disease, define the disease. Therefore, I think we are on fairly solid ground, if we use histologic criteria and morphometric criteria to identify a gluten reaction.

Certainly there are other criteria that can be considered such as clinical criteria and systemic, immunologic responses such as antibody responses, as well as interferon-gamma responses in peripheral blood. I am sure I'm forgetting something. Oh, there are other intestinal permeability studies.

There are actually quite a lot of biological markers that could be considered, but I think the field considers histology to still be not perfect, but the closest thing we have to a gold standard.

I don't know if Alessio or Dr. Collin would like to comment on this? No?

CHAIRMAN DURST: I think that summed it up very well.

(General laughter.)

CHAIRMAN DURST: Any other comments on that one?

(No verbal response.)

CHAIRMAN DURST: Yes, I think that was quite good.

REVISITING FOOD ALLERGENS

CHAIRMAN DURST: Okay. I think we have gotten through these questions. I did mention that we would like to address a few more points on the food allergens. A couple of the members have indicated they have some additional comments to make.

Erica, do you have one?

DR. BRITTAIN: I would like to say, I think I mentioned it earlier, more today but maybe even more yesterday that it seems like if there is a way for the information to be given, like, in terms of the allergic patients at least, that there are peanuts in it in some quantity," to have that information.

However, then there should be a second

threshold which is the threshold that the typical allergic patient has, "You are safe to eat it, if you are a typical allergic patient." Kind of like what we are hearing today about the gluten-free and the low-gluten.

For those patients who want to take the most conservative approach, they have the information that there is an extraordinarily low level of peanuts or whatever the allergen is.

There could be another standard so that a more typical patient could say this is the level that would be safe for them. To me that provides more information than a single threshold, which may be too strict for the typical patient and not strict enough for the most extreme patient.

CHAIRMAN DURST: Okay. I think Soheila has a comment.

DR. MALEKI: Soheila Maleki. I think it is a lot of difference actually between the two. In the case of peanut allergy or food allergies, the amount that you react to or the type of reaction you have can drastically change from one

exposure to the next. It is not even comparable. Plus, the consequences can be immediate mortality.

A celiac patient can decide the level they want to be exposed to or how much they can handle based on experience of having gluten-free food knowing that it is 20 parts per million or 200 parts per million. A peanut allergic person, if you tell them it is low peanut, they won't touch it.

You can pretty much ask anybody. I don't know if Anne is still here? She is probably gone. Any food-allergic person will tell you that if you gave them a low-, two-level thing that it wouldn't make a bit of difference to them at all, they would definitely not touch it.

DR. BRITTAIN: Again, I'm worried that whatever threshold, if it is a single threshold, it depends on how you want to set it. Do you want to set it for the most extreme person or those with almost no reaction? Then you are limiting the food choices of the more typical allergic patient.

DR. MALEKI: Soheila Maleki. I don't

think there is like a more "typical" -- a peanut allergic person would not eat anything that said "low levels of peanut."

CHAIRMAN DURST: Mark.

DR. NELSON: Mark Nelson. I'm thinking of your concept in terms of working with labeling and communicating with the consumers. My sense I that would be more confusing and, consequently, much less helpful than to have some threshold below which you could effectively label it "allergen-free" or there would be no consequences.

Now, that threshold may need to be different for different allergens, because of the severity of the response. I think that is really something that would be helpful for a consumer. Above that level, then, you would have to label the presence of the allergen because the typical consumer would respond.

DR. BRITTAIN: I mean, I know we heard today someone speaking in terms of the gluten, but she said, "I know you shouldn't label it," referring to the discussion yesterday, it would be

a disservice to most of the community if you set it at a level that is for the most severe."

That is what I'm concerned about. There are kind of two --

DR. NELSON: Yes. This is Mark Nelson. You're right, I mean, that is FDA's responsibility to set that number. I think that from a pragmatic and a practical standpoint and a workable standpoint, we might end up with something that was described about the hypoallergenic formulas for infants.

There is a confidence level that 90 percent of the population will not respond. That is where population is taking all of their nutrition from one food; their total food source is that. It serves the great majority of that allergic population.

In working with their physician, if they are part of that 10 percent where they do respond, then they just have to work harder to find a better food supply that they can accept.

CHAIRMAN DURST: Okay.

David.

MR. ORYANG: Yes. David Oryang. Yes, not being a biologist by background, just listening to the speakers yesterday and today, I can see clearly that in the case of gluten, it is easier to define the NOAELs. Those that have celiac disease are more willing to go for the challenge tests, because the symptoms are not acute.

I mean, they don't have acute signs, or I will say symptoms of disease, whereas with some of the other food allergens -- peanuts, and so forth -- I mean, if someone is going to suffer from shock, you are not as likely to go for those challenge tests. The data is not available in the more acute allergens as it is in celiac disease.

As far as our approaches are concerned, you see an analogy in that when you can't define the NOAEL correctly, because of no data out there, if you can't get enough subjects that are very reactive to come for the challenge test, then you can't get good data on the NOAELs.

Consequently, you can't set any safe

threshold directly using the safety approach, so you have to resort to other methods. With gluten and celiac disease, I think the safety approach seems to be a reasonable approach. If we can work on the issue of the uncertainty factor.

Because the challenge tests are there, I think there is some kind of agreement as to the parts per million. I mean, at least there are some values that we can see have already been established.

However, with the food allergens, I don't think that is really there yet, because not enough challenge tests have been done or can be done, so we have to resort to other methods.

I am just trying to look at it from a methodology point of view and just point out these differences, so that we can maybe think about it and see what other approaches can be used in specifically the food allergens.

I think the gluten, I think all of us have come to a consensus that the safety approach is reasonable, at least so far I don't feel

uncomfortable with it. In the other case, I think other approaches are better served.

CHAIRMAN DURST: Suzanne, did you have--?

DR. TEUBER: Suzanne Teuber. Again, in terms of the individual response, I think there is a greater uncertainty factor that applies to the individual in this case because of day-to-day variability. Again, those factors of exercise, alcohol, illness, unstable asthma all play a role.

We have absolutely no data on repetitive challenges for threshold in those threshold studies that have been done on whether there are differences in the circadian rhythm on the threshold, on the NOAEL or the LOAEL, in the few studies.

I think that food-allergic patients, as Dr. Maleki said, if there were any detectable there based on whatever limit the FDA chooses, those consumers will choose to absolutely pay it safe and avoid it.

They are not going to miss it knowing that, "Oh, it only had 200 micrograms that I could

have tolerated versus 2 milligrams that I would have reacted to."

They will be happy that it is labeled, that it had something, and that they can avoid it safely. It is a little different perspective of the patient than the patient with celiac.

CHAIRMAN DURST: Soheila.

DR. MALEKI: Well, I was just going to briefly say that essentially if it is not useful to the consumer then -- I mean, as Mark commented, the consumer, it wouldn't really help the consumer out so it is not something --

CHAIRMAN DURST: Okay. Any other comments?

(No verbal response.)

CHAIRMAN DURST: You mean we actually might finish up early? Oh, that's right, there was something left over from yesterday.

Steve, would you like to comment on question number two?

DR. GENDEL: Thank you. After caucusing with the rest of the Working Group, I guess what I

wanted to say in response to your question is we recognize that the questions and issues are not straightforward and they don't lend themselves to simple yes/no answers.

We listened to your discussion that occurred around that question and after the request for clarification. The Working Group believes that the Committee's discussion was responsive to the question and provided useful information to us, and we don't feel that there is any need for any other clarification.

CHAIRMAN DURST: Good. Thank you.

In that case, I will adjourn the meeting and remind you that we are beginning tomorrow at 8 o'clock instead of 8:30. See you at that time.

(Thereupon, at 5:20 p.m., the meeting was adjourned, to reconvene Friday, July 15, 2005, at 8:00 a.m., this same place.)

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