DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

# FOOD BIOTECHNOLOGY SUBCOMMITTEE (FBS)

of the

# FOOD ADVISORY COMMITTEE

Tuesday, August 13, 2002

9:00 a.m.

Harvey W. Wiley Federal Building
5100 Paint Branch Parkway
College Park, Maryland 20740

PARTICIPANTS

Acting Chair, Edward N. Brandt, Jr., M.D., Ph.D.
Executive Secretary, Dr. Margaret Cole

MEMBERS

Fred McDaniel Atkins, M.D.
Bob B. Buchanan, Ph.D.
Francis Fredrick Busta, Ph.D.
Anne R. Kapuscinski, Ph.D.

TEMPORARY VOTING MEMBERS

Jonathan Arias, Ph.D.
Douglas Gurian-Sherman, Ph.D.
Samuel Lehrer, Ph.D.

INDUSTRY SPECIAL LIAISON

James Astwood, Ph.D.

GUEST SPEAKERS

Paul R. Mayers
Dean Metcalfe, M.D.
Michael Pariza, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Welcome and Introductions

DR. BRANDT: Good morning and to those of you in the auditorium, we are glad you are here. We have a busy day. There are several announcements and then we will go around and let everybody introduce themselves.

First, tomorrow, we will start at 8:30 instead of 9:00. The Public Comment period will be moved to 9:45 a.m. tomorrow.

So we can introduce ourselves so everybody in the audience will know, I'm Ed Brown. I am the temporary chair, called back to active duty after having been retired. I am an old professor at the University of Oklahoma Health Science Center.

DR. ASTWOOD: I am Jim Astwood. I manage the Product Safety Center at Monsanto Company. I am the industry representative to this subcommittee.

DR. LEHRER: I am Sam Lehrer. I am at Tulane University in New Orleans. I am in the Section of Allergy, Rheumatology and Clinical Immunology.

DR. KAPUSCINSKI: I am Anne Kapuscinski. I am at the University of Minnesota. My home

department is Fisheries, Wildlife and Conservation Biology. I also direct Institute for Social, Economic and Ecological Sustainability. I have served on a number of other federal advisory committees, mostly the USDA, on biotech mostly focussing on biosafety issues. I currently also serve on the Global Environmental Facilities Scientific and Technical Advisory Panel in the area of biosafety.

DR. BUSTA: I am Frank Busta from the University of Minnesota, Professor Emeritus in the Department of Food Science and Nutrition. I am on the general advisory committee for FDA.

DR. ATKINS: I am Dan Atkins. I am an allergist with an interest in adverse reactions to foods. I am at the National Jewish Medical and Research Center in Denver.

DR. ARIAS: I am Jonathan Arias. I am a plant molecular biologist in the faculty of the Center for Agricultural Biotechnology at the University of Maryland Biotech Institute.

DR. GURIAN-SHERMAN: Doug Gurian-Sherman. I am the Science Director of the Biotechnology Project at Center for Science in the Public Interest.

DR. BUCHANAN: Bob Buchanan, University of California at Berkeley, Department of Plant and Microbial Biology. I am a plant biochemist.

DR. COLE: I am Margaret Cole, Food and Drug Administration.

DR. BRANDT: And the one that is going to run our lives for today and tomorrow, at least. If you have any questions about what is going on, ask her. Don't ask me, preferably. Now, back here, are all these FDA'ers. Stand up and be recognized.

MS. GLEW: I am Jeannette Glew. I'm with the Office of Food Additive Safety, Center for Food Safety and Applied Nutrition. I supervise and evaluate biotech submissions.

DR. MARYANSKI: I am Jim Maryanski. I am with our Office of Policy and Regulation. I help put together our biotechnology policy.

MR. LAKE: I am Bob Lake. I am the Director of Policy and Regulations here at the Center.

DR. BRANDT: And now we have a interloper from the NIH.

DR. METCALFE: I'm Dean Metcalfe, Chief of the Laboratory of Allergic Disease, NIH. I have a long-term interest in adverse reactions to foods.

DR. RULIS: I am Alan Rulis. I am the Director of Food Additive Safety in this Center.

MS. AINSWORTH-RAY: Hello. I am Karen Ainsworth Ray. I am a press officer here. Is a member of the periodical press sitting back here? Someone signed in periodical press. Okay.

MS. KRETSER: I am Allison Kretser. I am with the Grocery Manufacturers of America. I am the Director of Scientific and Nutrition Policy.

DR. PARIZA: I am Mike Pariza. I am the Director of the Food Research Institute at the University of Wisconsin, Madison.

MR. HINTON: I am Dennis Hinton. I am with the Office of Applied Research and Safety Assessment. We have been doing research in immunotoxicology for over twenty-four years for the Center for Food Safety. We are currently working on food animal models.

MS. FU: My name is Gigi Fu. I am with the FDA Office of Dairy and Food Allergy. I am a research scientist working on determining the severity of allergens and other food proteins.

MR. GENDEL: I am Steve Gendel. I am Chief of the Biotechnology Studies Branch of CFSAN.

MS. MacINTOSH: I am another interloper.

I am Sue MacIntosh from Bayer Crop Science. I am the Director of Regulatory Affairs and Regulatory Science in the Americas. But I am here particularly to give comments on behalf of HESI because of the Protein Allergenicity Technology Subcommittee.

DR. BRANDT: Dr. Cole?

Conflict of Interest Statement

DR. COLE: As I mentioned, I am Margaret Cole, Executive Secretary for the Food Biotechnology Subcommittee of the Food Advisory Committee.

First, I would like to read into the record the appointment of our temporary voting members. It reads, "By the authority granted under the Food Advisory Committee charter, I appoint Dr. Jonathan Arias and Dr. Douglas Gurian-Sherman as temporary voting members of the Food Biotechnology Subcommittee of the Food Advisory Committee for the August 13 through 14, 2002 meeting on food biotechnology," signed, Joseph A. Levitt, Director, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration.

Dr. Samuel Lehrer, as Chairman of the Committee for Allergenic Products in the Center for

Biologics Evaluation and Research, is appointed to serve as a temporary voting member for this meeting by the authority of Linda Skledani, Senior Associate Commissioner for External Relations, U.S. Food and Drug Administration.

The following announcement addresses conflict-of-interest issues associated with this meeting and is made part of the public record to preclude even the appearance of a conflict of interest at this meeting. All subcommittee members and temporary voting members have been screened for financial conflicts of interest.

Based on the agenda made available, it has been determined that the subcommittee will be addressing general matters only. The general nature of the matters to be discussed by the subcommittee will not have a unique or distinct effect on any of the members' personal or imputed financial interests. However, the following interests are being disclosed so the public can evaluate any comments made by meeting participants.

Dr. Frank Busta has been granted a waiver because he serves as a consultant to the food industry on issues not related to the topic of this meeting. Dr. Samuel Lehrer has been granted a

waiver because he owns stock in affected firms and holds various research grants.

We have asked all our guest speakers to complete a financial-interest and professional-relationship certification for guests and guest speakers to identify any potential conflicts of interest. Dr. Michael Pariza has a financial interest related to food-ingredient companies.

We would like to note for the record that Dr. James Astwood is participating in this meeting as a nonvoting industry special liaison acting on behalf of regulated industry. As such, he has not been screened for any conflicts of interest.

In the event the discussions involve specific products or specific firms for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

This meeting is being transcribed. When we reach the discussion portion of the meeting, please use your microphone and clearly identify yourself before speaking.

With that, I will turn the meeting back to Dr. Brandt.

DR. BRANDT: I notice he didn't appoint me. Anyway, I am here for whatever reason.

DR. LEHRER: Could I comment on that one point?

DR. BRANDT: Yes.

DR. LEHRER: To my knowledge, I don't own any stock in any companies that are affected by this. All I said was that I had TIAA Kreff and retirement funds and also mutual funds. I really don't have any idea what they own. I am afraid to know what they own, actually. But, in any event, just in terms of full disclosure, I would imagine that they own some pharmaceutical companies. I have no idea.

But, in terms of my personally owned stock in any of these companies, I do not.

DR. BRANDT: Any other statements? Any questions?

I want to alert the speakers that we are sitting up here with a timer. You have been allotted certain amounts of time at the end of which the gavel comes down, whether you are in the middle of a word. So, just be prepared.

Dr. Rulis?

DR. RULIS: Good morning.

[Slide.]

I am Alan Rulis. I am Director of the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition. My task this morning, in just a few moments, is to provide a bit of context for this meeting to point out that the work that this center does in regard to reviewing consultations, conducting consultations, with industry about new plant varieties that have been altered by recombinant and DNA biotechnology are actually conducted in the context of the Food Additive Safety.

So I want to tell you a little bit about that office so you know something about its makeup and its history and that will help you, I think, as we move forward with your discussions.

[Slide.]

Just to remind you that the Federal Register document that announced this meeting--the purpose of this meeting is to discuss science-based approaches to assessing whether new proteins and bioengineered foods are likely to cause allergic reactions in some individuals in order to assist FDA in developing draft guidance for industry.

[Slide.]

The Office of Food Additive Safety is laid out like this. I will take you through it a little bit so you will understand some of the makeup of it. This office is principally comprised of four divisions. You can see them across here. The historical roots of this office come out of this division, actually, the Division of Petition Review. It turns out that, in 1958, when the Federal Food Drug and Cosmetic Act was amended to require premarket approval of new food additives, FDA had to pull together a cadre of scientists who could evaluate data submitted to the agency by industry for the purpose of getting FDA approval for new food additives.

This division, historically, has had within it scientists of various backgrounds in order to do those kinds of reviews.

Actually, the same basic structure occurs in all divisions of this office, but let me just explain this one and then I will clone that, so to speak, into these other divisions. This division has within it three types of individuals; chemists who look at information about the chemical identity of the substances being added to food, the amounts

that people are likely to eat, information about the specifications and purity of those substances.

So we are really looking at the question of what is the substance and what is the human exposure to it. We also have toxicologists who evaluate, in this case, in this division, mostly animal feeding studies, traditional short-term of chronic feeding studies in animals, to look at the biological effects of food ingredients in living systems.

We also have a group of people who, in this case, we have called them regulatory groups, that are really, in government jargon, consumer-safety officers. They are scientists in their own right. They almost all have Ph.D.s in various fields and they are basically project officers. Their job is to manage the evaluation of petitions for new food additives, make sure that all the correct questions have been asked and all the correct questions have been answered and that there is an administrative record backing up all of the work the agency does.

So there is a linear process that anybody can go to and look at in writing that documents the agency's work.

Across the office, the basic makeup of these divisions in the same as that. It is a rather interdisciplinary group of these chemists, these toxicologists and consumer-safety officers. Almost everybody has a Ph.D. in one field or another from chemistry to biology, microbiology, molecular biology, pharmacology, toxicology.

The division of interest for your purposes this morning is this one, called the Division of Biotechnology and GRAS Notice Review. It turns out that, under the current statute, there is an exemption to premarket approval for food additives if the added substance is generally recognized as safe. So there is a class of substances we call GRAS ingredients--GRAS is an acronym for generally recognized as safe.

So they are evaluating not only whether a substance is safe but also whether there is a general recognition across the scientific community of that safety. In addition, they conduct the consultations with industry for crop products that are produced using recombinant DNA biotechnology, and they are looking particularly at the human health aspects of the injection of those crops, not the crop characteristics because that is the

purview of APHIS and USDA and not the pesticidal traits because that is the purview of the Environmental Protection Agency.

I will just point out briefly these other two divisions for your own edifications. This one is the Chemistry Research Division where there is research done on both what we call indirect and direct food additives--this is chemistry laboratory research--and an environmental group that looks at any National Environmental Policy Act considerations that are associated with any of our actions.

Down here is a division that is devoted to food-contact substances. Here we are looking at materials that touch food but that are not intentionally added to food. But, under the statute, we have purview over them.

[Slide.]

This, just for your interest, is a rather busy slide that shows the various areas that come within our purview. You can see we have interest in a whole host of different kinds of things that end up in food or contacting food. We look at direct food additives, sweeteners, preservatives, nutrients, fat substitutes and so forth.

Color additives in animal food, drugs and cosmetics, medical devices. That includes sutures and contact lenses, strangely enough.

GRAS ingredients, enzymes, fibers, proteins, lipids, sugars and so forth, going up to the upper right. Processing aids, antimicrobials, defoamers, ion-exchange resins, radiation equipment. It turns out that the statute defines the sources of irradiation for food as food additives. So we review these materials in order to ascertain that food that has been irradiated for microbial control is, in fact, safe.

Then we also, as I mentioned, just on that last division, we look at food packaging and food-contact substances. So coatings, paper, metal, recycled plastics, paper adhesives, and so forth.

And, in the lower left, foods and ingredients produced using modern biotechnology.

[Slide.]

Within the office, as you recall, I pointed out that the originating division was one that conducted premarket safety evaluations for food additives. But, in reality, a lot of our work is done under the rubric of notification these days. There are three notification programs

operating in the office. There is the one that we have instituted as a result of the 1997 proposal in the Federal Register to review industry notices to us that their product is generally recognized as safe.

We have a notification process that relates to food-contact substances and that comes out of the 1997 Food and Drug Administration Modernization Act. Then, we also conduct consultations on bioengineered foods.

[Slide.]

On the subject of bioengineered foods consultations, you are probably aware that, in May of 1992, the FDA published its policy on foods that are in the marketplace and including those that are the subject of recombinant DNA biotechnology and we, as a result of that and after that, began conducting consultations with industry since '94. Up until the present moment, we have conducted about 80, more than 80, of these consultations. About 50 of them have actually completed the process.

[Slide.]

If you go to our website and you double-click on the hypertext link in our website, I will

try to simulate that here, what you will get is this HTML screen. This is a list of completed consultations on bioengineered foods. It, in fact, explains what I just said about the '92 policy and talks about the consultation process and delineates the differences between what FDA does with these types of foods and what the Animal, Plant, Health and Inspection Service of USDA does and what EPA does regarding pesticides, and then proceeds to talk about the consultations that we conduct and the information that is in this website.

There is a lot of it. If you go to the website, you will find that there is a listing that contains the genetic modification. The actual gene or gene product is here. The source organism, the intended effect, the industry designation and then hypertext links to FDA letters to the company and in response to the consultation. So you can find all the information you need for completed consultations on our website.

[Slide.]

Just to bring you up to date, you probably are aware that, in 1999, the FDA held public meetings around the country to discuss its current consultation process. It received comments. In

January of 2001, we published, in the Federal Register, a proposal for making these notifications, these consultations with industry on crops, mandatory. We also made available some draft guidance, a notice of availability of draft guidance--that is, on the subject of voluntary labeling.

To this point, we have received over 100,000 comments that are currently being reviewed.

So I think that is pretty much my spiel. I just wanted to be sure that you saw the work with this subcommittee within the context of the office. I hope I have made that clear. If there are any questions, I would be happy to take them at this time.

DR. BRANDT: Questions.

DR. GURIAN-SHERMAN: Doug Gurian-Sherman. I would like some clarification, one, on the premise of the meeting, itself. You mentioned, in the Federal Register Notice, that the purpose is to determine or avoid--not your words--a protein likely to cause allergenicity. I guess I have a question as to how that relates to the FFTCA's standard of reasonable uncertainty of no harm. It would seem that you are flipping somewhat the

burden of proof in terms of the level of certainty that you are looking for when you say that it should be likely, or identified as likely, to be a food allergen, that reasonable certainty of no harm seems to suggest the opposite.

DR. RULIS: Let me say this. I purposely did not launch into a discussion of our legal framework because I think could take up a tremendous amount of your time and it would be probably be derailing the purpose of the meeting to do so. I think it is certainly something you may want to discuss as you go forward, if it does appear to be needed.

But I think it would probably not serve purposes of this committee so well to get into the legal questions. I think the purview of this committee is scientific, as I understand it, and I am going to defer to Bob Lake momentarily to give the charge and to talk about his view of what you are here to do and put that in the context of charge and questions eventually.

But my reading of the current charge and questions to this subcommittee are really not legal ones. They are scientific ones. We are looking for your scientific input.

I would say, just in brief response to your point, that we have had in place for a long time premarket safety evaluate scheme for new food additives that uses the reasonable certainty of no harm standard. That is in place and, for some situations involving biotech foods, it is conceivable that a protein would be introduced in such a way that the appropriate modus operandi would be to go through the premarket approval scheme and use the reasonably certainty of no harm standard.

But that has not been the case for the vast majority of biotech foods that have come before us. In that context, we are looking more at the food in the context of other foods. The question before us is as it as safe as its counterpart food, as safe as is really more the standard we are using there.

But we have open the possibility of using the reasonable certainty of no harm standard. I think to get into a discussion of the interstices of that standard probably would not serve us well this morning.

DR. KAPUSCINSKI: Anne Kapuscinski. It seems somewhat obvious what would constitute the

end of a consultation for biotech foods but I am curious because you said that there are 80 since 1994 but 50 have been completed. So what is the difference between one that is completed and uncompleted. Why is there such a big difference?

DR. RULIS: It may be that, at some point in the consultation, we are asking for a package of information to cover the corrections we might have. If the company decides, at some point, that they don't have the information that we are asking for, they may decide to withdraw.

DR. KAPUSCINSKI: So is the consultation completed when either the FDA says, "This looks fine; you can go forward with it," or the company decides to withdraw and just doesn't want to do any more consultation?

DR. RULIS: We look at the package they have come in with and ascertain whether we think all the relevant questions have been answered to our satisfaction, that they have dealt with all of the necessary aspects of it. If they have, in our mind, then we will write them a letter that basically says, "It is your responsibility to market a safe product. You have brought before us your--you have laid out before us all the questions

that you have dealt with and your answers to them. We have looked at them and have no further questions at this point."

DR. KAPUSCINSKI: Okay. Thank you.

DR. BRANDT: Any other questions?

DR. BUCHANAN: I have one question. This is Bob Buchanan. How many products do you see on the horizon?

DR. RULIS: I can tell you that, at the moment, under the rubric of biotechnology, the number has actually fallen off somewhat. There was an initial burst of several dozen and then, in fact, if I could easily put this HTML screen back up there, which I can't, I would show you that, in 2001, there were a couple and, in the Year 2000, there were a couple. Most of them were 1999 and before.

So it struck up a bit. But that is not necessarily a prediction for the future in that I know that there is a likelihood that there would be some new developments on the horizon that would bring more forward. But, at the moment, we have had a slight lull.

DR. BRANDT: Mr. Lake is now going to tell us what we have to do.

Charge and Questions

MR. LAKE: My name is, again, Bob Lake. I am the Director of Regulations and Policies for the Center and, as such, represent Center management for this meeting and, in that capacity, let me first welcome all of you, to the Food and Drug Administration, to the Center for Food Safety and Applied Nutrition and to our new building in College Park.

Biotechnology is, obviously, a very important topic for a lot of reasons. The issue of allergenicity is also important across the board, irrespective of biotechnology. When you get the two together, you have a particular set of very interesting issues and it is very important. It is not new. I expect that long after we are done here, there will continue to be many discussions.

So I would like to, I think, first talk a little bit about the context of this meeting, sort of where it fits in and also a little bit about what may happen in the future.

In the first place, just a little bit of context, and you will hear a lot more about this, but we had a Food Advisory Committee meeting back in '94 dealing with the issue of allergenicity and

biotechnology. So that sort of got us started.

We have, through the consultations that Dr. Rulis was just talking about, gained some experience that involves our thinking on this issue. In addition to that, as you can well imagine, this is seen as a very important topic internationally and we have been actively participating in an effort about a Codex Alimentarius Commission to grapple with a number of issues that relate to evaluating the safety of bioengineered foods including allergenicity.

You will be hearing more about that as the day goes on as well. But we have been active participants in that process.

We think we are at a place where it is time for the Food and Drug Administration to put down on paper, and make public, something we call guidance. This is a document that serves several purposes, or will serve several purposes. One, it is, in part, guidance to our own people on how they evaluate the information that is coming in. It is also guidance to the industry. It tells them what it is we are going to be looking for so that it is guidance to them on what kind of work they need to be doing.

It is also an articulation to the public about what it is we are doing and why. Under our current procedures, we have to develop something called draft guidance, publish it for public comment and then come back with final guidance.

We think we are at a point where it is time to begin the drafting of that guidance. But, before we do it, we would like to, in effect, bounce some ideas off of this subcommittee. So you will getting a lot of information this afternoon and tomorrow and then we will be asking you to give us some feedback.

We will be using that feedback to draft, do what I will call a preliminary draft, of guidance. We will then be getting back to you at a future meeting to actually have you look at our preliminary draft before we go public with it. So, one of the things I want to leave with you is we are not going to ask you to solve the whole problem is this meeting and, indeed, I think as the science develops, as we get different kinds of submissions in the figure, the policy will have to evolve.

But, what we are for primarly now is to articulate something that is based on the experience that we have had with the kinds of

submissions we have been getting and that we expect to get for the next few years.

We will, if it hasn't already been handed out, be handing out shortly a copy of the charge and questions. You can read that at your leisure and there will also be an opportunity, before you begin your deliberations tomorrow, to look at that in some detail. So I am not going to spend a lot of time on that.

I simply wanted to give you the idea that what we are really asking you to do is to consider the various pieces of information that you are going to hear in conjunction with your own knowledge and to give us some feedback that will assist us in putting together some draft guidance, or some preliminary draft that we will then show to you at a future meeting before we go public.

At least, that is our current intention. Also, as a part of what we are going to be asking you, we would like you to spend a little bit of time, to the extent that you can, identifying areas where research is needed, either research that we can do or others could do, that would put is in a better position and, perhaps, help us to evolve a better policy, a more definitive policy, for the

future.

So those are kind of the two big things. What are kind of your thoughts on what we say now, what kind of research we ought be doing and then, to the extent that you can help us, because part of our document is going to be an explanation to the public what we are doing and how we do it. If you have got any ideas on how we can do that well and in a way that the public can best understand, we would appreciate your thoughts on that as well.

Having said that, and I think that is probably enough to say before you actually have heard very much of what you are going to hear, it occurs to me that because this is the first meeting of this committee, most of you are new to us and we are certainly new to you. So I guess I would like to--I was going to ask the Chairman's permission to do this, but since he is not here, I will take the liberty of inviting any questions that you have about this center, either our structure, our philosophy, what it is we do, things that help you understand why we have you here.

But, really, at this point questions not about biotechnology or allergenicity because others will talk to you more about that, but questions you

have about this place, this organization, who we are.

So let me stop and invite your questions on that.

DR. BUCHANAN: Bob Buchanan, again. How much research do you do? I really don't have a feel for that.

MR. LAKE: Research is a component of what we do. Quite frankly, it is not as large a component as we would like. Again, our budgets are appropriated by Congress. Our colleagues at NIH is the place where most of the research as it relates to the public health ought to be done, so we don't get a whole lot of it here.

But we do some. But a lot of the research we do is focused on helping us to do the other part of our job which is enforcement. We make these kinds of decisions, but we also have the day-to-day enforcement responsibility. That requires that we have methods of analysis so we have a fairly large effort devoted to that for all of the different things that we are responsible for.

But, to the extent that we can, we do as much research as we can do but it is limited. Now, you may also know that the University of Maryland

is within walking distance and we do, even before we came out here, had created with them something called GFSAN which is a collaborative research activity.

We also have some other collaborative efforts where we, in conjunction with other academic institutions, try to get some leverage on some research that is helpful. But, the general answer to your question--again, I have to confess, I have never been in a laboratory except to visit. That is not my background. But it is something we consider important.

DR. GURIAN-SHERMAN: Doug Gurian-Sherman. What kind of relationship do you have, let's say, with NIH in terms of giving them input into what kind of research would be done, I would imagine NIH is more focused on basic research and your interest is, in part, trying to get input that will help you make regulatory decisions? Do you have any formal working relationship in terms of that?

MR. LAKE: I actually don't know the answer to that question. Again, research is not the area that I am involved in. It is more policy development and regulation. But I know, in general, our philosophy is to collaborate with

anybody we can collaborate with to get at the information that will help us in making our decisions.

Let me also comment on your previous question. I think, at least to some extent, in some of the further discussion, there will be some more description of--as we talk about how we go about our current business that may help answer your earlier question.

DR. BRANDT: Other questions? Yes, ma'am?

DR. KAPUSCINSKI: I have a question about how you really make operational coordination under coordinated framework. So I guess I am curious, when an issue such as allergenicity comes up, if there is a difference of opinion between FDA and, let's say, EPA that was involving a crop that might be producing a compound that has questions of allergenicity but it is a crop that fits under EPA's purview, how do you resolve the differences and is there--even though I have studied all the coordinated framework laws, it is never really clear to me if there is one law that preempts another or whether the agencies have some other process for reaching the actual decision.

MR. LAKE: A couple of comments around all

of that. One of the challenges that all of the agencies are grappling with is that the statutory framework that we all are using did not contemplate biotechnology.

So we are all making do with statutes that already exist. It is a challenge. I mean, it is a challenge, to be perfectly honest, as somebody who has done this for a number of years, before, even internally within a single center such as CFSAN. When you reach out to other parts of the agency, it is a bigger challenge and when you go to other agencies is it still a bigger challenge yet. But it is very important. We take that seriously.

I think we have not had the kind of conflict that you are describing, those kinds of differences of opinion. I think largely the reason for that is that the responsibilities, even though it is a coordinated framework, if you look very carefully, the responsibilities for each of the agencies is distinctly different.

So, while we want it to mesh, each is doing a separate piece. For instance, APHIS has the responsibility to oversee what is going on in fetal trials, et cetera. They do not make judgments and don't even want to make judgments

about whether any of these foods, if eaten, would be safe to the person who eats them. That is not their focus.

By the same token, we defer to them in terms of their oversight of fetal trials and then whether things are properly contained, et cetera. There is more likely to be overlap between FDA and EPA because we actually make similar kinds of judgments.

But, actually, the division there is that what they look at are pesticides that are genetically engineered in food. With regard to the pesticide, itself, we defer entirely to EPA. They actually have a strong statutory framework for pesticides. So if they decide that a protein that is genetically engineered to be a pesticide in corn or soy or whatever, if they make a decision that it is unsafe, we accept that because they do that process.

What we look at--we look at two different kinds of things with regard to those crops that are genetically engineered to contain a pesticide. As I said, we defer to EPA on the thing that is the pesticide in the crop. What we look at are what are the other changes that occur in that and is

there anything about those other changes that would give us concern.

They, in turn, defer to us on those questions. There are, of course, other things that come to us--again, I think you will hear some more about them--that don't have anything to do with pesticides. So the food-safety question is entirely one that we grapple with and that the other agencies both defer to us.

At the same time, we do try to be sure that are policies are consistent. The most recent example is the OSTP document that relates to low-level presence, unexpected presence, of food things in other foods. Again, that was something that we, in an interagency context, under the leadership of OSTP, have been working on for quite some number of months.

Hopefully, that gives you some answer to that question. Again, I think some of the later presentations may touch on that a little bit more.

DR. BRANDT: Very similar to resolving differences between two departments in a college or a university. About the same thing.

Any other questions?

Thanks very much. We have this document.

MR. LAKE: You should have it.

DR. BRANDT: Tomorrow afternoon, one of the things that we will be talking about are the three questions at the bottom of Page 1 and the top of Page 2. So you might start thinking about those. They are not particularly in order of importance, but, certainly, the first two are the ones that they need a lot of help on. The last one, if you have thoughts, why that will be great.

MR. LAKE: Absolutely. Again, as I step down, let me again express my appreciation to all of you for taking time out of your busy schedules to be with us during these two days. Again, this is the beginning, hopefully of a series of meetings, at least one of them being on this topic but then other meetings down the road as well.

I will be here throughout the day. If any of you has any, again, organizational kinds of questions or questions about this place, feel free to talk to me. I think it is okay to do that.

DR. BRANDT: It is up to you.

MR. LAKE: I will try to answer those questions. The other thing I am involved in is implementation of the new bioterrorism law. I have a meeting at the department tomorrow that I must

attend but I will be back for tomorrow afternoon for the deliberations.

Thank you very much.

DR. BRANDT: Thank you.

We will now take a break for approximately twenty minutes. Dr. Metcalfe, you will be prepared to go about ten minutes ahead of time. That doesn't give you ten extra minutes, however.

[Recess.]

DR. BRANDT: We are ready to begin. Dr. Metcalfe from the National Institutes of Health is going to give us his presentation on basic food allergy background.

## Basic Food Allergy Background

DR. METCALFE: Thank you.

[Slide.]

As I was just kind of talking to Dan before I started the lecture, this is a nuts-and-bolts food-allergy lecture. A couple of committee members, maybe more than two, could take over this. I can show them how to advance the slides. They could give this.

I actually have a lecture on how the decision-tree thing, and everything else--I was hoping to be able to do that because then I

wouldn't have to put all these slides on power point. But Jim is going to cover that and I am going to cover the nuts-and-bolts of food allergy. This power-point presentation is really off of slides that go back a long time because, in terms of the basics of food allergy, we haven't seen a lot of new things to put into this lecture.

I will try to update you on some of the classification and things of that sort, but it is a fairly direct lecture and hopefully, it will be helpful to those of you who don't think about allergenicity.

I am going to try to make a few comments about things that you--I am anticipating some questions as we go through on certain areas of this and then, hopefully, I will have enough time to take questions at the end.

[Slide.]

Now, the standard definitions, two standard definitions, that we work under in this field are here; food intolerance is really anything abnormal that you experience with a food that somebody else does not. That is everything from a lactase deficiency, meaning lactose intolerance, to a true allergic reaction to a food.

We generally use the word food hypersensitivity as an abnormal reaction resulting from a heightened immunologic response to glycoprotein components within foods. We could specify that a little bit more if we talked about food allergy. Generally scientifically, we would be moving toward an IgE mechanism. To the lay public, there is not much difference in these definitions.

[Slide.]

One way to look at the spectrum of reactions to foods on an immunologic basis that not everybody experiences is this kind of diagram. Some of the stuff that I am going to show you is from an ILSI-sponsored classification approach to disease, particularly with infants, that can be extended to adults that was published a couple of years ago.

So you can kind of go from an IgE to an non-IgE mechanism in these reactions. Most of those that will concern this committee will be IgE based. Those are the classic immediate hypersensitivity reactions, hives, asthma, gastrointestinal problems and anaphylaxis after exposure to a food in an immediate sense, within a

few minutes.

Oral allergy syndrome is an immediate reaction largely confined to the mouth. We will come back to that. Atopic dermatitis is listed in the middle because it has an IgE basis but other things in that person experiencing that reaction move toward eczema. But what of what is known about IgE reaction, particularly published by Hugh Sampson, has been actually in challenges of children with atopic dermatitis.

Then there are other diseases such as allergic eosinophilic esophagitis, gastritis and gastroenterocolitis that have a strong IgE component. Clearly, there is something different going on that we don't understand from a strict IgE reaction.

Then there are non-IgE reactions, virtually exclusively observed in infants and children, dietary protein enterocolitis, proctitis, enteropathy and then celiac disease which you will have to think about, but, since we have a better idea of the active components, that is an easier problem to handle, we think, in terms of moving new proteins into foods. You would probably not move the proteins responsible for celiac disease. That

is a more obvious question.

[Slide.]

So let's start out with the typical genesis of an IgE-mediated reaction, the immediate responses that we are most concerned about. The steps are well described. You have to have some exposure to the antigen at some point in your life and then TH2 cells, that is kind of a TH2 phenotype, an allergic phenotype, cells that tend to make things like IL4 and IL5 rather than gamma interferon, collaborate with antigen-processing and these cells to make IgE which then becomes fixed to high-affinity receptors on the mast cell and, for that matter, the basophile surface.

Then, on re-exposure of antigen, there is release of mediators. That is the allergic response. It has been an amazingly difficult response to fine-tune details about or, for that matter, to thwart. There is no, for example, specific drug known that specifically inhibits mast-cell degranulation and the regulation of IgE synthesis has been very difficult although some approach is now talked about such as anti-IgE removal from the system so you could have some promise.

Now, if you talk about the amount of antigen required to sensitize, which comes up in these committees all the time, the answer is probably it doesn't take very much if somebody is of the TH2 phenotype. You could show that in animal models where you can dose-response sensitization and, if you use intraperitoneal or intramuscular, then it is easier to sensitize. If you use certain adjuvants like alum, you could get more IgE.

Then, if you use TH2-responsive animals, in mice and rats, for instance, it is easier to sensitize. So you put all that together and what that means is that the ability to sensitize to certain amount of allergen and the threshold is going to vary on the individual, vary on the protein, vary on any adjuvant effects.

The end of that is that it has not been possible, really, to set a level below which you can assure that someone will be sensitized. In an extreme case, somebody with the TH2 phenotype, highly allergic, genetically predisposed to react to certain antigens with breaks in the mucosa or inflammatory valves or wherever you want, would be sensitized whereas if would never happen in anybody

else.

In terms of the amount of antigen to elicit a response, it is a dose response. Generally, in food allergy, it takes large amounts. It take milligrams to grams. But there are exceptions. When you look at those exceptions, like Steve Taylor has done through the Food Allergy Research Program and some of the industry-sponsored things he does, you start looking at thresholds in a feeding, particularly infants or young individuals, of about a microgram. But that is very rare. You can count those cases.

But if you try to set a threshold and you get down to that microgram level, in reality, what is going to protect most things in this system and most people in this whole system is that a few things are allergenic and it is awfully hard to sensitize and it is awfully hard to precipitate a reaction.

But when you try to set numbers for thresholds, then you run across huge problems. So that is IgE-synthesis mechanism and a few comments about how difficult it is to set regulatory guidelines based upon what we know about it.

[Slide.]

Now, prevalence data. This is typical prevalence data. It is more than existed ten years ago. These are a number of studies that have been published. I picked them out fairly at random. Here is one, food Allergy intolerance where they sampled and challenged of 2.4 percent. This would include a lot of things that are nonallergic. 1.3 food-allergy adults, by Woods et al. This is very typical of what you see in the literature.

1.1 percent food allergy in children and adults together to tree nut and peanut. This is a random digit-dial survey specifically limited to these two substances. So intolerance in infants and children at 8 percent, if you look within that, about 2 to 3 percent are IgE-mediate. Milk intolerance, the first three years, 2.5 percent.

What does all of this mean? It means generally that in children, IgE reactions often transient, can be seen in 2 to 4 percent of children, somewhere in that ball park, and, in adults, it is somewhere around 1 percent. A lot of those reactions can be handled.

But, if you look at the total numbers, now, you are talking about in the United States somewhere in the neighborhood of 40 or 50 million

people, potentially, that could be affected through these IgE-definitive mechanisms. so it is not a small number of people. When you look at the percent of the total population, it looks small but, in aggregate numbers, it is large.

[Slide.]

Now most food allergens, as you well know, are glycoproteins. They tend to be 20,000 to 40,000 molecular weight. These are rough guidelines. They tend to be protease resistant. They tend to be acid resistant. Let me just speak to that for just a moment.

This is usually, at least over the last ten years, have often been discussed in the context of digestibility. So you eat something and, if it is resistant, then you are more likely to absorb it and become sensitized or provoke a reaction.

It is not clear to the structural biologist who studies allergen structure whether that is really the issue or whether or not it reflects something about the tertiary structure of the antigen which might be more important. For instance, it might have more to do with antigen processing in a macrophage than it really has to do with digestibility. My comment here would be think

about acid and proteases in terms of resistance to degradation and don't argue about whether or not something can be digested in the stomach in the stomach acid of one, fasting, resting and go into that kind of discussion.

To me, this is really just a characteristic, a relative characteristic. It is not absolute and it just kind of generally can be used in an assessment program. It has been overused and underused. I know you will probably discuss this more.

Then there is the whole idea about whether or not linear or discontinuous or continuous epitopes and all this are the active component in food allergy. Hugh Sampson would argue that many of the true food allergens are allergens that provide linear fragments of molecule that can provoke an allergic reaction. He will argue with that.

But there is also evidence that when you lose the tertiary configuration, that some things lose their allergenicity. So probably both are going on.

[Slide.]

The most common food allergens, and you

can expand this list, but in children, it is generally peanut, milk, soy and egg. In adults, peanut, crustacea, crayfish, lobster, crab, shrimp, that sort of thing. Tree nuts, fish and eggs. Now, some people would add to this, for example, sesame and the Europeans like to add celery because it causes a lot of oral-allergy syndrome.

You can expand this list but this accounts for about 90 percent of reactions. A major allergy within this is an allergy within one of these proteins that causes more than 50 percent of the reaction. So those are two rough definitions.

Again, what I think probably saves most of us as much as anything else from getting a food allergy is that is hard to be wrong no matter what you do because of the ability to find people that are truly allergen that you can reproduce on challenge is fairly--is not that common.

So what happens is that you can have a lot of strategies that appear to work because of the frequency of these reactions when, in reality, it really has nothing to do with it and that has a lot to do with controversial techniques, diagnostic techniques that I don't think you will get into. But here are most common food allergens. And I

will get into the how you make a diagnosis.

[Slide.]

The diagnosis is both subjective and objective. Subjective; history, diet diaries, elimination diet. So history is a big thing that doctors use; were you the only person that got sick, did everybody get sick. Look at epidemiologic factors. You can send people home with diet diaries and say, every time you think you get sick, write it down, what food you are eating. Then they come back with a long list. They are so happy because they found other things they are allergic to and you are so distressed because you had enough to worry about before. So we don't use them a lot.

Elimination diets really is something that used to be used more than it is today because you don't want to send people home and say, "Well, reintroduce this food," and have them anaphylax at home. So they have to be used very cautiously. So, really, history is the big one here.

Objective is cutaneous testing and then measurement of allergen-specific IgE by RAST and ELISA. Leukocyte histamine release where you take leukocytes and sensitize them or leukocytes from

the individual and challenge with antigen is rarely done just because it is technically more cumbersome. Then there is double-blind food challenge.

I am going to go over just a few points about some of these very quickly for you. Cutaneous testing can be used for raw food or purified allergen from food. The general method is to put a drop of this substance on the skin, tint the skin through it and then look for a local allergic reaction characterized by itching, redness and a wheel formation, and then their policy, generally, but they are more of a control which is just diluent and you have to have a positive histamine to skin test to show the person is not suppressing antihistamines and that sort of thing.

Fairly direct, simple. Does identify specific IgE in the skin. Relatively safe, although people who are strongly allergic to something like tree nuts, you probably would not test them this way, for instance, or peanuts. So you occasionally have to worry about severe reactions.

It is hard to skin test if somebody has widespread eczema and this sort of thing. So

sometimes you have to go to in vitro diagnostics. Here is the important one. They are not diagnostic. In other words, some of you in the room probably have skin tests to foods and eat them without a problem and never realize you have a positive skin test.

The same thing for pollens. It is not a mystery to food. Some people do have a ragweed-positive skin tests and won't have a clinical sensitivity. But, the other side is very unusual. It would be very unusual to have somebody who had an anaphylactic reaction to peanut to have a negative skin test.

So, they confirm your suspicion but they cannot work in the absence of an evaluation that looks at history and other features. It cannot be used in isolation.

Now, can it be used for everything? No. If you are worried about something that might be a chemical that might act as a haptene so it has to bind that body albumin or something before you have a reaction or be degraded, you wouldn't pick it up on a skin test, so it doesn't work, for example, as a general technique for pharmacologic agents.

You have to be very careful when you use

it because you can easily get a negative skin test but the person could still be allergic after that material is degraded or act as a haptene or something of that sort.

RAST and ELISA have gotten very good. They are almost as good as skin tests. You can kind of quantitate how much IgE there is to an antigen and, generally, the higher they are, particularly the Pharmacia cap system which has been widely studied, the stronger the results are, generally there is a correlation with more severe reactions. But you can have a low cap and anaphylax to peanut and have a high cap and anaphylax to peanut. But there is a general correlation.

They measure antigen-specific IgE in the serum. They are a little bit more costly. They are somewhat more remote. Again, they are not diagnostic for the same reasons I went over with IgE testing through skin tests. The same caveats apply to positives and negatives.

[Slide.]

Double-blind food challenge is not done very much. Doctors don't like to do it in their office because it is cumbersome and they put the

patient at risk so only those people really comfortable with it do it. If you put it into a safety assessment, you have to get IRB approval. Today, at least at my institution, that would be hard. It would be hard to do that.

So it is a wonderful test in terms of it is kind of the gold standard for people who say they are allergic to food. It simply involves putting food somehow or other blinded in capsules or in a liquid where they can't taste the food. You start with small amounts and then go up to a regular feeding.

It is diagnostic if positive. Occasionally, I think that there are reasons why you can get a negative and miss it on food challenge. Those are not that common. It is very difficult work to do with multiple sensitivities. But, the bottom line is that this is a technique which, while straightforward, would only be used when the patient wouldn't be put at great risk, when you can resuscitate if you have a problem and the patient agrees.

In the doctor's office, you can elect to do it. If you are doing it at a scientific institution, those people who have done it for many

years without a problem, like Hugh Sampson, say it is getting very, very hard to get approvals to do these kinds of things, at least currently, in the current IRB--it is just a fact of life.

[Slide.]

Now, the differential diagnosis, I will not go through. It is not the purpose of this slide. But just to let you know, if you are a physician and you asked to look at somebody who flushes after they eat shrimp, there are other reasons. It could be a lot of histamine that grew from bacteria contaminating the shrimp or something of this sort.

If somebody had bloating or something, it could be an enzyme deficiency like lactase deficiency. If somebody had pain when they are swallowing, it could be esophageal cancer for all I know. So you have to use some common sense here. You have to look at what else can mimic the symptoms and make sure that you are dealing with food allergy and not another disease. This results in the common recommendation that people who think they have food allergy really need to go through a doctor and vet it because you would be surprised what kinds of diseases hide under food allergy and

people don't realize it.

[Slide.]

Food additives. Food additives have generally not been associated with allergic reactions. There are four here I list. You would almost have to talk about every one of them. Sulfiting agents went through the FDA many years ago. If you inhaled the gas sulfiting agent, SO2, you could provoke asthma.

There were examples that perhaps a few people recognized sulfite bound to serum albumen as a haptene. This is not a major problem any more since rayon spray-on sulfites were banned, but there are still a lot of people that think they are sensitive to sulfites.

With tartrazine, monosodium glutamate and sodium benzoate, most of the time we are talking about something associated with chronic hives. This probably doesn't happen very often. It may be real. You are going to see a lot of confusion as you go into the literature about chronic hives, what causes them. This is because it is so hard to put somebody on a diet and then challenge them in a situation where you can be sure that the result is--the hive that comes up is a result of the

challenge. It is very hard to design these clinically

So you will have people claiming that 50 percent of the people that they see are sensitive to additives, which is not true, and you have other people say they could never identify, they are probably missing few. Somewhere in here is some truth, but it is not very common. Anaphylaxis to these agents is virtually nonexistent even though tartrazine causes anaphylaxis. I don't know who documented this.

DR. BUSTA: I have heard a lot comment on flushing. Is that equivalent to hives?

DR. METCALFE: Flushing is simply cutaneous vasodilatation, vasodilatation of your surface vessels. I can happen when you exercise. It can happen when you get embarrassed. Some people have prominent flushes in the face and upper chest. It depends on your ethnic background and your age.

Flushing can result from allergic reaction when histamine is released. Many other things can cause it. It has been proposed for sulfiting agents. You can get a vasovagal reaction that causes flushing. Flushing is very nonspecific and

frequently believed to be important and often is not.

But, that being said, it is one of the things that goes along with the systemic allergic reaction. But other things that physicians look for, like conjunctival irritation and things like that, that we like the signs of systemic anaphylaxis better than flushing.

[Slide.]

Controversial diagnoses. These are the kinds of things you see in the literature that are due to foods or not. There is very little evidence that these are due to foods and I don't think we will get into these except that, when you see people come to talk to you about these reactions, you have to ask them to specify their allergies.

If somebody comes in and says, "I am here because I have allergy to such-and-such, and they don't describe what that is, you need to ask them because, every once in a while, they will say, "I get tired," or, "I have psychotic episodes." It helps define what their definition of allergy is.

All too often, you just assume, oh, allergy. They are having hives and anaphylaxis. But, when you ask them, it is far different. So

just a warning about that.

[Slide.]

Now, let's talk about oral-allergy syndrome. This is IgE-mediated disease. It is believed to be certain people eating fruits that often have antigens that cross-react with pollens and latex and other things can eat certain fruits and vegetables and they get burning and swelling and itching in their mouth.

The proteins implicated are heat-labile food and vegetable allergens, often cross-reacting with some polyallergens and latex cross-reactivity, believed to be IgE-mediated, generally destroyed by cooking or by digestion and frequently seen in people who have allergies.

Rarely do these allergens cause a systemic reaction but, occasionally, they do. They are very labile allergens and most skin-testing materials do not pick them up because the allergens are degraded in the bottle of the extract with a lot of proteases and things like that.

So, again, when you looking at prevalence of allergen diseases, a lot of European papers, in particular, will add oral-allergy syndrome and the numbers go way up. You have to just be careful of

that. This is generally considered to be less of a problem than the more significant food allergies, but it does exist. It is a problem for a lot of people and you need to know about it.

[Slide.]

Anaphylaxis is the signs and symptoms resulting for IgE-mediate mast-cell and basophil activation leading to the release of chemicals whose target organs are primarily such things as blood vessels, smooth muscle. The site of mediator effects may be local and remote from the site of allergen ingestion or exposure; for example, you could have a skin test to peanut right here, but you would have systemic circulatory flaps.

In other words, it goes from here everywhere. Anaphylaxis; some people distinguish anaphylaxis from anaphylactoid which is the clinical signs and symptoms of anaphylaxis but we either don't know the mechanism or it is not IgE mediated. Today, most people just say anaphylaxis and say most of it is IgE-mediated and worry about the rest later.

But it is life-threatening. It is the major problem that we worry about with food allergies.

[Slide.]

This is some data from Hugh Sampson's extrapolation of the number of people who might die in the United States every year from food anaphylaxis. He took the frequency of anaphylaxis in Denmark. He looked at the number of patients seen in the Mayo Clinic experiences foods, did an extrapolation, came up with 2,500 cases a year in the United States with 125 deaths.

It is ball-park figure. It could be off by 100. Who knows? But it just gives you an idea that it is not that frequent but does exist and it is what you worry about. The cases often make the newspapers. They are highly visible cases, often tragic cases, involving healthy children and heart-wrenching when they occur. But their numbers are not great.

[Slide.]

Fatal food-induced anaphylaxis. This is an early study. There are plenty of studies. I picked this one up, both males and females, all ages. Almost all these people are atopic. It usually happens away from home when they don't know they are eating. Peanut is a big provocateur. Often they die because they have had no epinephrine

early. The other risk factor is asthma. Most people who die from anaphylaxis have asthma. So it is a pulmonary death.

These are the features of anaphylaxis that have to do with foods. There are a larger series, but these are the basic determinants of it.

[Slide.]

The diagnosis of an allergy, or an allergy-causing anaphylaxis is the presence of allergic signs and symptoms, hives, angioedema, trouble breathing, et cetera, acute hypotension and/or upper or lower-airway obstruction. Often, people develop laryngeal edema, can't breath. That can lead to demise.

Absence of conditions in the differential diagnosis. Elevated levels of mast-cell tryptase release by mast cells where the serum can be used in post mortem. Exposure to agents known to be associated with anaphylaxis or the patient would have a history of anaphylaxis without knowing the cause.

So those are basically the nuts and bolts of anaphylaxis.

[Slide.]

The treatment of IgE-mediated sensitivity

remains avoidance and prepare to treat inadvertent exposure. If you are severely affected, you were a medic-alert bracelet or a device to notify people if you are found unconscious. You give yourself epinephrine upon exposure to something that you are anaphylactically sensitive to. You may take antihistamines or seek medical help.

Unproven. We don't have any way to desensitize to foods. It is recognized that there are no prophylactic medications that reliably prevent. So, really, the problem, then, for us in the field and with you is that the prime protection for people that may have food allergies or may develop them is simply avoidance. That goes into labeling which we are going to talk about. That goes into what is going on here.

[Slide.]

Novel approaches to the treatment of food allergy being discussed; anti-IgE antibodies. This takes a lot of IgE out of your system, may make you less sensitive. There are some trials going on. The hope would be that a child extremely sensitive to peanut taking IgE would have to ingest more peanut for a reaction. So it would lower their risk and that may well be the case.

There is vaccination with plasma DNAs to induce responses that are protective. Antiallergic immunostimulatory sequences that are supposed to promote interferon gamma. We will talk about these if you want. The concern there is that if you go from a TH2 to a TH1 response, instead of allergy asthma, you end up with Laker's granulomatosis or something.

But there are all concerns about these approaches. Immunotherapy with mutated proteins and peptides so that you get a new response without the risk of a reaction. All of those are being looked at now and we can talk about them if you want. There is nothing I see that is really going to protect people, at least within the next five to ten years, I don't think. So we are stuck with what we have.

[Slide.]

We have covered this clarification. Now we are going to briefly cover some of the others. I am going to go through these very rapidly. Allergic eosinophilic esophagitis is carried mostly in infants and children. It is such things and emesis and failure to thrive. The proteins implicated include cow's milk. There is an

eosinophilic infiltrate. Poor correlation to skin tests. The treatment is protein elimination and, you can see here, sometimes steroids.

This is a disease which is really of interest to pediatricians now. We have learned a lot more about it. We don't know a lot about it right now, but this is what we do know. It is largely limited to infants and children. One of the themes--I will come back to it in a minute.

[Slide.]

Allergic eosinophilic gastritis is more likely to be IgE-mediated. This is associated with vomiting, abdominal pain, failure to thrive in children. Many of the cases are atopic. Many have peripheral eosinophilia. Age of onset, neonate to adult. Proteins are the common allergens that we have talked about.

Eosinophilic infiltration in the gut. Elevated IgE, although about half you can't find skin-test specificity to. The other half have multiple positive skin tests to foods. There are probably two populations in here. Atopic predisposition is possible. Treat with steroids and try to structure a diet.

We are studying this. Anti-IL5 will make

these patients better somewhat, for instance. These patients tend to be of a strong TH2 phenotype, at least to orally ingested allergens.

[Slide.]

Gastroenterocolitis is basically the same thing affecting more of the intestinal system. You add things like colonic bleeding, protein-losing enteropathies, but you still have the eosinophilia, elevated IgE. Many that have skin-test response. This is a fairly unusual disease.

[Slide.]

Dietary protein enteropathy. The rest of them that we are going to talk about don't have an IgE basis are seen primarily in infants and children. They often outgrow the disease. If it occurs in adults, it is hidden within things like inflammatory-bowel disease and we certainly don't know about it.

They are caused by proteins. There are no known animal models. There are no known diagnostic tests. The reason I am showing you these is because, no matter what you decide to do about a food, it may be done for you. You can't do much about these because we don't know much about these and so that is why we have always focused on IgE.

So, in a child, diarrhea, malabsorption, failure to thrive, anemia, edema. They get quite ill. No increase in evidence they are of an allergic phenotype. Food challenge can result in vomiting and diarrhea. Age of onset, up to two years.

Here are the proteins implicated, common foods that children often eat. Pathology is dramatic, often small-bowel injury, intraepithelial leukocytes, et cetera. No food-specific IgE. You eliminate the offending allergen and then they outgrow it.

[Slide.]

Same for dietary proteins; colitis, diarrhea, vomiting and anemia, failure to thrive, hypotension, villous injury, colitis, fecal leukocytes, no food-specific IgE. With food challenge, there is believed to be an increased risk of hypotension and shock and then basically there is an elemental formula until they start to outgrown this problem. Most of these go away.

[Slide.]

Proctitis; basically, the same idea, limited to the rectal area. It is not clear what is going on here. Probably cells that are

sensitized are homing to the gut and are causing disease in this area causing proctitis.

The same kind of idea; fecal leukocytes. No role for IgE. Again, a fairly rare disease.

[Slide.]

Celiac disease I mentioned early. Everybody knows about this disease and pretty much knows how not to create a new food that would cause celiacs to have a problem. Manifestations are chronic diarrhea, diarrhea and failure to thrive in infants. Age of onset typically more than six months. The protein foods implicated are wheat, rye and barley, primarily. Pathology is a villous atrophy and there are certain characteristics of certain kinds of lymphocytic infiltrates.

Certain antibodies that can help in diagnosis. Treatment is elimination of gluten associated with certain HLA patterns. Lifelong history. There probably is a lot of gluten sensitivity that may be one allele instead of two or something that is really not picked up. There may be a lot of subclinical celiac disease.

But, at any rate, this, on the surface, would appear, at least to most people, to be something that a company simply would not create by

moving gluten into some new foods. So I don't think this has even been a major issue, but it must be remembered.

[Slide.]

So, again, this is really what we can worry about plus atopic dermatitis. These are unusual diseases, but they do have an IgE component. These are non-IgE-mediated disease, granted more rare, granted mostly in infants and children and very difficult to deal with.

DR. PARIZA: How much atopic dermatitis is due to food versus other causes?

DR. METCALFE: In adults, it you look at the series, it is rarely associated with the digestion of foods. So, in adults, atopic dermatitis is very difficult to associate with foods. In children, it is much more common.

DR. ATKINS: About a third of children with atopic dermatitis have a food that will trigger it, is one trigger.

DR. PARIZA: How do you know that? Do they eat a food and then they get it? Is that the way you see it?

DR. METCALFE: Yes.

DR. ATKINS: Generally within two hours

ingestion of the food, they develop flushing at the sites.

DR. PARIZA: Oh; within two hours?

DR. ATKINS: Sometimes much quicker than that, but they develop flushing at the sites of excema and start to scratch and, the next day, they will have a rash.

DR. METCALFE: An awful lot of what is in the literature that tells us about food allergies is atopic dermatitis studied by pediatricians. If you look at most of the literature that you are going to base your decisions on, there is very little evidence from adults. It is almost all pediatric data.

Why are we interested in this?

[Slide.]

I am going to show some people from the lab to jus kind of candid shot of our lab. You may have seen this before.

So, I think we have time for questions.

Questions of Clarification

DR. BRANDT: We do have. Questions? Anybody?

DR. LEHRER: Sam Lehrer. You had mentioned the figure of 40 to 40 million Americans.

Did you mean have the potential for allergic responses or that have food allergy?

DR. METCALFE: Let's talk about that data. It is only 1 percent to 2 percent that we think really have it so that is something like 4 to 6 million. If we look at the people that think they have it, then you are talking about 40 million. I'm sorry; I should have made that clear and I am glad you asked that, because the problem that you deal with in this area is an awful lot of people that think they are sensitive but relatively few that do.

But, still, if you talk about 1 to 2 percent, you are talking about 4 to 6 million people in the United States. That is a huge population. But if you look at perception, it is huge.

DR. LEHRER: I would agree. Of the 1 to 2 million that have a food allergy, this is all of the food allergies that we see. They don't all react to peanut. They all don't react to shrimp. So, if you take one of the major food allergens--I guess peanut would probably be a likely candidate--how many people are you talking about, if we are taking the worst allergen that we know of?

DR. METCALFE: That is an interesting thing to ask. That is a good question. Let's say we have 1 percent of adults who have true food allergy. This actually goes back to stuff done many years ago. If you look at what most people react to as adults, it is going to be peanut or tree nuts or a little bit of crustacean. Most of those people react to one allergen, something like 60 percent.

So one could, right away, say, out of that 1 percent, probably half of those individuals, maybe more, are reacting to one allergen that is probably going to be peanut or tree nut or crustacean. Then you get another 30, 40 percent that take in the rest of them and start to have multiple allergies.

Then you have a very small number of people that seem to be reacting to everything. We are not talking about oral-allergy syndrome here which puts up the numbers. We are talking about generally. Dan, do you want to comment on that? You have thought as much about this as I have. Is that fair?

DR. ATKINS: That's fair. You could go to the telephone surveys that Ann Furlong and her

group have done. They have got sensitization on both adults and kids to peanuts and tree nuts. I think, in children, it is supposed to be about 0.5 percent and, in adults, it is supposed to be about 0.7 percent, if I remember right.

DR. BRANDT: Those are true, or those are responses?

DR. METCALFE: That is just a random digit-dial survey with a high screen. Those are undocumented.

DR. LEHRER: The ones that are reacting, seem to react to everything. I know you said it is a very small group. Do you have any idea--are you talking about 0.1 percent?

DR. ATKINS: I don't think it is that high. If you look at the number, probably you pick up--so, 50, 60 percent, one. Another two; you probably pick up another 20 percent so that puts you up to 80. Maybe three or more, another 10 or 15 percent. Beyond that, you have multiple reactors. So it is a very small number. It is probably--you are right; it is 0.5 or less in the population.

DR. METCALFE: But the point is, it can change over time. There are children who become

sensitized to multiple foods; milk, eggs, wheat, soy and then, by the time they are between five and seven, they may lose sensitivity to two or three of those foods, peanut sensitivity or--

DR. LEHRER: But just to get some kind of handle on numbers.

DR. METCALFE: That's in adults. If you look at children, it is more frequent. The percentage goes up to 2 to 3 percent and it is heavily weighted toward milk and soy. Those sensitivities are generally lost. It is very hard to identify an adult that is allergic to milk or soy. It is just hard to find.

DR. LEHRER: If you eliminate the milk and soy and you ask for a percentage of children, what do you think that would drop down to?

DR. METCALFE: I don't know; about 0.25 percent, maybe? Dan?

DR. ATKINS: Again, 90 percent of allergic reactions to foods in kids are milk, eggs, wheat, peanut, soy. By the time kids are five to seven years of age, they tend to outgrown sensitivity to milk and wheat and soy and egg and then you are left with peanut, tree nut, fish, shellfish.

DR. LEHRER: So I guess the question would

be of the five-to-seven-year age group, what percentage?

DR. ATKINS: We think it drops from about 6 percent in young kids and infants--infants and young children--to about 1 to 2 percent in adults. The majority of that occurs over that five to seven years early on.

DR. METCALFE: A lot of these reactions are not life-threatening, either. Not everything causes anaphylaxis. So it is a spectrum, just like all allergy is, to pollen or anything else.

DR. ATKINS: The point I want to make, though, is that it not concerning to the people who have it. If you talk about oral-allergy syndrome, they are still very affected by that. There are foods that they can't eat. Then, if you take a food and it is not digestible, or we change it so that it is not digestible, and that patient eats is and now it gets to the lower gastrointestinal tract whereas, before, it was digested above, you may have a group of people that are anaphylaxing who weren't before exposure to that food.

DR. METCALFE: The difficulty in this is that 1 to 2 percent of the population is not a small number of people. Then, if you take that up--and I am

glad you asked that question because we are really talking about a couple of million people here. When you look at the people who think they are at risk and you have to get through that chaff.

But it is not a small problem. Of course, no company wants--I don't want to speak for a company--but no company wants to create something that is going to put them into court and put them out of business. I mean, things like silicon breast implants would pale by the consequences of putting out something as sensitive as peanut into the general population. Monsanto or one of these companies would be out of business, I think.

So, everybody, for various reasons, wants to protect everyone. But there is a real risk out there.

I want to catch a couple of other questions. Yes, sir?

MR. HINTON: Not to change the subject but, in any case, I was wondering if you would comment on the potential of animal models in terms of the mechanisms of allergenicity and so forth because one of our charges will be in that area in terms of the mechanisms in animal models being similar as to what we see in humans.

DR. METCALFE: I give you my view on animal models because--let's talk about practicality. First of all, any reasonable animal model is going to have to use a small animal like the mouse, I think. I think dog models and beagle models and pig models are just not reasonable.

When you go into those animals, then the purpose of an animal model would be to rank-order things that are allergenic in the population, from something non-allergenic to allergenic. Here, I don't have any--I would recommend you not recommend think about trying to mimic human disease, that it has to be orally fed, that it has to happen on oral challenge, but simply that you have an animal that can rank order allergens for a given class of allergens. That is my own feeling about it.

If you said the only animal model we can use has to result from oral sensitization without and adjuvant and provoke a reaction on oral administration, I think you are going to have it extraordinarily difficult to make an animal model.

But if you said, I am going to take a certain mouse with a certain background that responds to a certain profile and I am going to see if, on the basis of skin-test reactivity or IgE

synthesis or something, rank order those things roughly to what humans see, then I would say, yes; that should be possible.

If you are asking for a single validated model, there is none. I would even predict, if you started to see some animal models that worked with some protein classes, they wouldn't work with all protein classes. I, personally, don't think you are going to ever see one validated model. I could be wrong.

And, no matter what happens, it is never going to be like a toxicology assessment. I don't ever see it being perfect. This is something we have discussed for ten years and I have just given you--it needs to be worked on, and I applaud those people who are trying to do it.

DR. BRANDT: Why don't we stick here to the subcommittee members.

DR. METCALFE: Oh; all right.

DR. KAPUSCINSKI: This is Anne Kapuscinski. When you were talking about the grains that are known to cause celiac disease, you made the comment that it would seem that no one would want to introduce genes from those into other foods. But how about if you were to actually

engineer wheat or barley or oats? How much do we know about our ability to predict whether that would accidently increase the allergenic reaction or broaden the percentage of people that might get exposed? What do we know about that?

DR. METCALFE: I, personally, don't know the answer to that. But it would seem to me that, because you know what the active ingredient is, that one of the things you would ask for is a measurement of the level of gluten. That can be determined. But, certainly, you would want to know that, that you didn't upregulate its expression.

You could go one step beyond. You could actually go into a crop that is not known to produce gluten and actually ask if it starts to.

DR. KAPUSCINSKI: Right. I guess I was thinking, also, not only the level of the gluten but do we know enough about the structure of the gluten? What about the structure is really causing an allergenic reaction to know if there could be subtle changes, again, in its three-dimensional tertiary structure that could broaden the range of people that might--

DR. METCALFE: There is a fair amount known. But it is unclear enough to make me worry

about trying to get down to the peptide sequence. There are known peptide sequences that cause the disease and bind to certain HLA groups. But there is enough noise in the background to say that you don't pick up everything with that that I would personally recommend a different way to look at it which would be overall to measure gluten or glutenagen or something which would have, within it, the active peptides.

But you should go to somebody that studies this to ask that question. If there is somebody that knows more about that, please comment. But that would be my own feeling about that.

I just reviewed this because I just reviewed a chapter written on celiac disease, just yesterday. That is my read on the current state of the art.

DR. GURIAN-SHERMAN: I guess the question I have with the current kind of passive reporting system, and I am talking about a postmarketing issue, what do you feel the likelihood is--you mentioned that companies would certainly be concerned about liability--but the likelihood that some of these conditions would be reported if they are occurring at a fairly low percentage of the

population and nobody is actively looking for it in the population.

DR. METCALFE: I think it is hard for a passive reporting system to do a good job of looking for reactions. I think it works to a degree if you follow up case report challenge or something to really find out if you have somebody sensitive.

The difficulty is that if you had something that was causing the problem that was in a common protein source and then got into other foods, people developing a new reaction would have a hard time identifying where it was coming from. So that while it has a value, I think everybody recognizes the limitations.

Then there is the other side. Once you publicize something, then everybody starts saying, oh, now I know what causes my headaches. So it has a value but, in my own judgment, it is seriously flawed.

I think we try to teach all allergists that, if they have somebody coming in with something that they are reacting to that they take by mouth and it is unclear what that is, then they should think about what might be novel in that food

and then they can make extracts of that food and do skin testing.

There are ways to try to get at the answer, but I think it is very difficult for the individual, unless you have engineered a blue peanut and people say every time they eat a blue peanut, they react, "And I don't react to regular peanuts."

But that is not the way it works in reality. Then, for a lot of places in the world, there is no label. You buy from street vendors and stuff. So, really, the way to keep the genie from getting out of the bottle, I think, is to try to do a good job on the front end, not the back side. I think that is what everybody worries about.

Did you have something, Bob?

DR. BUCHANAN: Yes; I did. Bob Buchanan. I think I need to rise to the defense of the dog. While not wanting to cover the earth with canines, I think that the dog has its place in testing, at least according to current evidence. It is the only animal model that I know of that has allergies similar to humans including clinical symptoms.

We have an article under review now in JACI, Journal of Allergy and Clinical Immunology,

that shows that there is a hierarchy, just as there is in people. So I think that it may behoove a company or another interested party to use that as a test if they are not satisfied with rodent tests. I think the cost of that would be totally insignificant compared to what has happened--so I think it is something that should be considered.

DR. METCALFE: You have a point, Bob. They do have a role. Since I will be leaving this room shortly, and you will be staying in, I am sure that the dog--

DR. BUCHANAN: I am not as persuasive as other Virginians have been, but thanks.

DR. ATKINS: This is Dan Atkins. In reviewing source materials, there appear to be two different approaches. One is the weight-of-evidence approach. The other is the decision-tree approach. In reading these articles, you have been involved in the development of decision trees. I was just curious, before you leave the room here, if you could give us your impression of the two different approaches and the pros and cons of both.

DR. METCALFE: This is, of course, a huge problem. It is a huge question. I would say this, that if you have a decision-tree approach and you

have defined points where something is rejected from consideration, then you are going to make mistakes sometimes in rejecting something you shouldn't. That is going to happen.

But what it does from a committee standpoint is it give you, in essence, some cover. On the other hand, the weight-of-evidence approach should work as long as--but it puts more responsibilities on the committee. Very few things are absolute in this decision process.

The only thing I would say is a weight-of-evidence approach actually puts more of a burden on a committee and the FDA to look at the weight of evidence and make a balanced approach. It may, in the end, be preferable. I don't know. But, from a committee standpoint, it really makes this committee extraordinarily important because there is no automatic rejection at certain contiguous amino-acid sequences, unless you decide.

There are no automatic rejection points so you can set that bar as high or as low as you want it. Then, from a committee standpoint, you really have to know what you are doing so you will understand the difference between a protein made with E. coli and protein expressed in a plant and

all these other subtleties.

If you don't know that, then you may miss critical decision points. So my general comment is I have no problem with it but I do think it makes committees like this extraordinarily important in the portion in which they look at data.

Does that answer your question?

DR. LEHRER: Another point that I wanted to clarify that I think is very relevant to this committee in our discussions is the amount of food--and I think we need to consider it in terms of not the food, itself, so much but a protein, in terms of sensitizing individuals and also the amount that can provoke a reaction. I know this is a tough question for all the reasons that you mentioned in your presentation, but could you go over that again?

I wrote down it was milligrams to grams, but--

DR. METCALFE: If you look at, for adults and for many children, the amount of food that you have to eat orally that contains the allergen--I am not talking about purified allergen--is usually in milligram-to-gram amounts. It is a reasonable amount of food in terms of being able to measure

it.

But if you look for cases where people have used purified allergen or the lowest amount of a compound food that would cause an reaction, you will find cases at the 1 microgram level. So, if you try to set a level below which you can't provoke a reaction under any circumstances by oral feeding, it is probably going to be at one microgram or less.

Some people have argued for 10 nanograms. But, of course, you are talking about the absolutely most sensitive child or infant. I don't know if other people want to comment on this but I get very comfortable at the 1 microgram level.

In terms of sensitization, you really have a huge problem here because cross-reacting allergens can be, in part, sensitizing. So I don't think it is possible to set a level. I think if you use a 1-microgram level for provoking, I think you just accept it for sensitization. But probably sensitization is a much more complex procedure.

For instance, we all know the tropomycin is a major allergen in shrimp. It is also in cockroach. Shrimp and cockroach are more closely related, as you well know, Sam, because Sam has

done a lot of a work on this. So sensitization may be much more complex than just things that you thought you had eaten.

So sensitization, I think, is an enormously difficult thing to try to address. I would only be relevant if you said, if this stuff is in less than X number of nanograms that it won't sensitize somebody. If you had to reach for a figure there, I would probably think in the microgram, nanogram, range but I would have a hard time defending that.

DR. LEHRER: Can we glean any information out of the foods that we know are major allergens and the eating habits of the population; for example, something like peanuts, which are exposed at a relatively young age in large amounts in the American population as opposed to maybe other populations and which seem to be such an important food allergen.

DR. METCALFE: There are general things you can say. As a population, in general, is exposed to more allergens, peanut or whatever, the reactions to that go up. So there is an association with exposure.

But if you go down to the specific, you

will find cases of children who had their first peanut and anaphylaxed and you don't know where they got sensitized. Those are the two polar ends of it.

DR. ATKINS: The point is about 70 percent of kids who are allergic to peanut have their reaction on first known injection of peanut. So the point is that they are probably sensitized through breast milk, mom ingesting peanut butter while she is breast feeding, sensitizing her. At least a large percentage are sensitized that way. That is what we think, unless there is some cross-reacting allergen out there that we haven't picked up yet.

So, again, if you are talking about sensitization, the amount is small.

DR. METCALFE: This is really the issue in children particularly. If you look at adults who, let's say--but there are a lot of cases of adults who, in their twenties or teens, first get allergic to shrimp and they have been eating them regularly. So they have probably had a whole lot of exposure before finally something happened and they lost the ability to regulate IgE to it.

In children, though, it is very clear. I

would take that data and say that it is very clear that nanograms to microgram levels are sensitizing those children.

DR. ATKINS: Right. Again, you have got a special case here. Their GI tract may not be mature. Their immune system is not quite mature.

DR. LEHRER: In those children that are sensitized, possibly sensitized, to peanut via mom's breast milk, have those moms been shown to be eating high doses of peanuts or is there any correlation with that at all?

DR. ATKINS: I am not aware with a correlation with dose.

DR. LEHRER: Nothing is known about it?

DR. ATKINS: In regard to tolerance, we don't know if it is a small amount fed frequently or larger amounts at intervals.

DR. METCALFE: Then there is the argument because this is genetically predisposed, do we do children a disservice, on an epidemiologic basis, if we don't expose them to small amounts when they are children to tolerize. So you have a counterargument that, if you go overboard on this, that you will get more children sensitized and there is evidence for that.

There is evidence that more children get sensitized to peanut when their mothers stay away from peanuts breast feeding, at least one study I know of. So it is a moving target, really. It is very difficult to make absolutes in allergic diseases.

There are generalities that we know. I think the more we know, the more difficult it will become. It is not that we are going to find something out that is going to solve this problem. The more we find out, the more difficult the problem has become over the last decade. So that is why I think, going back to Dan's question, that people have gone after the weight-of-evidence approach, because, with time, absolutes seem less absolute. But it does mean that the committee does has to very informed.

Can I take one question back here?

DR. BRANDT: Yes.

DR. METCALFE: You had a question?

DR. PARIZA: I was just wondering. I heard several of you say something about outgrowing these allergies. What is the cellular or molelcular basis for this. Does anybody know? Do the plasma cells die off? What happens?

DR. METCALFE: No. It is tolerance. What happens is you tolerize yourself through regulatory t-cells and other things. There are a lot of ways to tolerize and specific mechanisms in the specific instance you could give. But your global question is difficult.

Let me just make this point. You have a child sensitive to milk and they have an IgE response. Then, when they grow up, they are no longer sensitive to milk and they probably will not have IgE to the milk most of the time and they will not have a TH1 response. They don't see the antigen.

So if you look at--take something we know more about, say, ragweed. If you look at people that are not sensitive to ragweed, they do not have a TH1 response to ragweed with gamma interferon production. They have no response. They are TH0.

The problem with most of these strategies is to try to counteract the TH2 with a TH1. What you really want is to take a TH2 and make it TH0. That is a very important concept because when you start overproducing gamma interferon in response to an allergen, then you start to get other kinds of diseases.

DR. KAPUSCINSKI: I appreciate your concerns about labeling. Do you think, though, that there is any other kind of approach for postmarket monitoring like some kind of planned epidemiological tracking that could be done that would still allow us to gather some information after the fact? I guess I am interested in sort of pressing on that because, given your last comments about the fact that the more we know, the more complex it is and the fact that there is not a very good chance we are going to complete a magic-bullet answer, every time I think about that, in risk assessment, I find myself thinking, well, clearly, then the most useful package for risk assessment or risk management would be to make the best up-front decision but then follow up to see if what we thought was our best decision really was so, and sort of prepare ourselves for--be better prepared for surprises or problems, detect things before it really gets out of hand.

DR. METCALFE: This is the best question you could ask and the most difficult question to answer because you could start out with a dramatically different approach than is used for foods. You could take a new product and you could

say it has to go through clinical trials, you have to feed people that might potentially be sensitive. How many would you have to feed? Thousands and thousands.

And then you would have to say that, we don't see a response, or, nobody got allergic. Then you would release it. So that is one side of the coin.

Then, if you don't want to do that, which is extraordinarily difficult and no one wants to get into, really, at this point in the world, then you have to say, we are going to release it into the population but we want to monitor for reactions. The only way you can do that is to know who it is released into, tell everybody to look for the reactions, particularly physicians, and raise the awareness of this.

Of course, you get a lot of noise. There are a myriad problems with that approach. But you could do it. Labeling, I think has a role. It has a role in protecting against allergens in general and it is always debatable, in terms of genetically engineered foods because foods lose their identity.

But there are people and places and groups that have decided that labeling, they are going to

try for good, bad or indifferent. I think it has a role. People would have to decide what that is. I wouldn't be so bold as to say that. But that is the way you would have to do it.

Then kind of the third tier down is to say, well, let's just have people self-report if they have a reaction. Most of the time, they don't know what they are eating. They don't know if something new is introduced. That makes it as a kind of safety assessment, very, very weak.

So those are, really, the three broad things I think you are asking.

DR. BRANDT: There is another problem that most all epidemiologists have, having been one at one time, and that is that, once you let it be known that you are out looking for something like this, you will get flooded with people. The classic case of increasing the incidence of tularemia in Arkansas by a hundred-fold simply by announcing that they were going to go out and look for it.

Almost everybody that had seen a rabbit had tularemia. It is very difficult to do that postmarketing if you announce in advance that that is what you are going to do.

DR. LEHRER: Just a quick question about physician follow up on reactions or reported reactions. A patient comes into his office and it is difficult to identify. One of the real problems, as I think you alluded to, is reagents and availability and knowing how to trace things.

Do you think that, perhaps, if a panel of these reagents was made available so this could be used for testing such patients, this would be a useful way of following it in a controlled environment as opposed to--

DR. METCALFE: By reagents, do you mean the genetically engineered form, raw extract, or do you mean the genetically engineered protein purified?

DR. LEHRER: No; the raw extract. The extract in terms of whatever is being used as a component in the food.

DR. METCALFE: There is a certain value. I don't know how practical it is. If somebody came into your office and said, "For the first time, I am reacting to corn." And you said, okay; you found out that that was engineered. So you say, all right, I can call away to a certain place and I can get an extract of that corn. I can get an

unengineered in that corn, too. I can skin test. Yes; I think that has value.

Whether or not it is practical, because there are so many things engineered, I don't know. And I don't know how you vet it and purify it. I don't know about liability and I don't know how you would set up the system. But there would be a certain value.

If you think about the way people make skin-test extracts, I don't think that they are paying any attention, engineered or not, right now. You go get a corn extract from Hollister Steer, they are going to the supermarket. They are buying what is on the market.

They are not saying, wow, this is genetically engineered corn. So, the stuff in the bottle, most of the stuff, if it is engineered from corn, it has already got the stuff in it.

DR. GURIAN-SHERMAN: It would have to be updated over time as they are introducing new proteins.

DR. METCALFE: The way that extracts are made, if you talk to people at Hollister Steer, they used to send the technician down to the supermarket. That is the way they do it.

DR. ATKINS: The other thing, though, is that these extracts are unreliable for fruits and vegetables. So if you are talking about corn, you would have to have them bring in the corn and make up a fresh extract.

The point I wanted to ask you about is you made it sound like challenging humans with the food was going to be impossible because you would have to challenge so many people. But, to me, we are going to make the jump from animal models and serum testing to releasing it out into the public and basically exposing everybody with that.

So, just like we are contemplating here looking at serum reactions, why wouldn't we take the population of patients that we would think would be at highest risk and feed them the food and see what happens in that group.

DR. METCALFE: Let me be clear. First of all, Dan, I didn't say not to do it or it was unreasonable. I just said it is an option that people have looked at and decided that they don't want to do for various reasons. For a lot of regulatory reason, statutory reasons, practical reasons, everything else, this has been an approach that has not been institutionalized.

My guess is that is not the purview of this committee. But you could have a real think tank about this and look at the pros and cons of it. There are ethical issues. If you don't have to eat an engineered food, a lot of the Helsinki rules become a problem, as you know, because you then have to put people to a risk that they might, arguably, never have in the real environment.

I don't say that that is not a hurdle you can't get over but when you start to look at this issue, there are a lot of things that you have to discuss before you would institutionalize such a procedure.

I am not saying I am against it. I am not so sure some day, in the future, people might not do this if there is a huge error made in screening these crops.

DR. ATKINS: To me, the logical problem is we are going to take people that agree to do it and have read the pros and cons, and we are going to take that stuff out and feed it to the public without informed consent. I don't understand that.

DR. BRANDT: Let me ask a question. For seventy years, we have been genetically engineering foods by hybridization and cross-breeding,

selective-breeding, all the other techniques and we haven't seen much as a result. There have been new corns put out all the time, for example, new beans, new strawberries, that are not being done in the lab but are being done by people out--grafting and doing other kinds of things that people like that do. Being a gardener, I have bought them many times.

Yet, the allergic responses to those, and the allergens--and there you are doing very gross transfers and it would be easy to transfer almost anything--we haven't seen all of this that I know of. What is the evidence that, over the years, we--I doubt if you can buy a food on the market today that was there seventy-five years ago, that isn't genetically engineered.

DR. METCALFE: I wouldn't argue with your premise. I would say that it shows you that most of the time that you do traditional plant breeding and most of the time, fortunately so far, it looks like all the time, when you approve something that is genetically engineered, you have not had a true allergy created that caused a problem.

It doesn't mean that it won't happen tomorrow. That is the problem.

DR. BRANDT: Yes; I understand that.

DR. METCALFE: Obviously, the number of things that cause true allergies are fairly circumscribed. For all the reasons I have said, there are a lot of alternative practices of medicine. You can say, "I have a food allergy," and they will put you on a light box and they will give you acupuncture and you can get better. A lot of things just aren't real.

So what you really are looking is the fact that it is fairly uncommon and it protects you and gives you layers of a kind of security that has nothing to do with your intellectual prowess or the scientific prowess or just the odds of creating something that is going to be allergenic is going to be unusual.

DR. BRANDT: One more question.

DR. ASTWOOD: Jim Astwood. Dr. Metcalfe, how do you feel about, given some of the slides that you showed that a lot of the anaphylactic reactions that result in death, particularly, are due to unexpected exposures? That is basically when someone stumbles across peanuts, they are peanut-allergic, and they didn't expect it to be there.

Given what you just said, and given the public-health dimension, how do you feel about current methods in terms of their adequacy to identify important current allergens?

DR. METCALFE: Jim, are you talking about--see, a lot of these cases are where a child ate something that wasn't supposed to have peanut that did. So it becomes an issue of how clean are the food lines, what are the thresholds. It seems to me that the big problem here is that the existing guidance is not followed in most of these cases.

DR. ASTWOOD: Right. So, for us, for the biotech folks, how do you feel about our ability--when we are thinking about moving a specific gene from one food to another, how do you feel about the methodologies that are available to actually identify and prevent, or identify, "Ah; that is a peanut allergen or that is a kiwi allergen?" What do you think of those categories of methodologies?

DR. METCALFE: The one thing you can do is not transfer a known allergen. You know you can prevent that.

DR. ASTWOOD: Would you say that we have adequate methods to do that?

DR. METCALFE: Yes; you have the methods

to do that. What you don't have is when you get into the gray areas of bringing in, expressing more protein from some source like some soil bacteria or you bring in an allergen from something that people commonly don't eat, or you are worried about changing something in its endogenous expression, or you are worried about some other unintended consequence in some other protein.

That is where the real difficulty is. And we know that. I think this committee--I don't think you are going to see that. Nobody is going to say, well, we have engineered this tomato to express peanut storage proteins that are allergenic. Why would you want to do that?

DR. BRANDT: You wouldn't sell it, probably.

DR. METCALFE: I don't think you are ever going to see that.

DR. LEHRER: If you do, you will never sell another tomato.

DR. BRANDT: Let's go to lunch. Then we will reassemble here at 1 o'clock.

[Whereupon, at 11:30 a.m., the proceedings were recessed to be resumed at 1:00 p.m., this same day.]

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

[1:00 p.m.]

DR. BRANDT: We are ready, Dr. Pariza.

Safety Assessment of Enzymes and Protein Ingredients in Foods

DR. PARIZA: Thank you very much. I am very glad to be here today.

[Slide.]

I am going to talk now about determining the safety of microbial enzymes used in food processing.

[Slide.]

There is a little bit of history that I would like to begin with in describing this to you. I got involved in this area since the early 1980s and we published, really, three successive improvements, I would say, on the original concept as things evolved since then.

But, back in the early 1980s, there was a considerable problem, both within industry and within FDA, of how to determine the safety of enzymes. The problem is that an enzyme that is used in food processing is not a single entity. It is really a gemish. It is a ground-up organism of some sort that happens to contain the enzyme

activity that you are after.

There might be some modest amount of purification that goes on but, in no sense, would it be the kind of instrument we would take in the laboratory to study enzyme kinetics or something like that.

So the question was there were general rules, or general regulations, that said that enzymes could be derived from microorganisms as long as they were nonpathogenic and nontoxogenic. But then they listed various organisms that could be used, one of them Bacillus cereus, for example, which we know is a pathogen that produces toxins.

So the issue was how do you go about determining that, in fact, these enzymes are safe. So we began, in 1983, Mike Foster and I--it took us about three years actually to come up with the paper that was ultimately published. I want to say that Pete Reed, who is now deceased but who then was the chief microbiologist of FDA, was quite helpful in developing this as were the industry people, in developing the initial concepts.

In 1990, the concept was expanded to include microorganisms that were genetically modified and then, most recently, in 2001, we

published the latest version of this which now takes into account the potential for protein engineering.

So I would like to discuss, then, each of these and lead you to where we are today on our thinking.

[Slide.]

The first paper that was published in 1983, the focus was for enzymes produced by traditional methods from microorganisms, plants and animals. Plants and animals didn't present much of a issue because these were enzymes being derived from plants and animals that were already considered food.

So the focus quickly became, really, primarily in microorganisms. We considered a number of issues by way of discussion points. The first and foremost is the safety of the production strain which we refer to as the source organism with particular regard to toxigenic and pathogenic potential of those strains.i

We came to the conclusion that the enzyme, itself, should not be focus of toxicological evaluation because the enzymes that one is using in food processing are carbohydrases or proteases or

enzymes that already have--so the focus, we determined, should not be on the enzyme, itself, because the enzymes that one typically uses in food processing are not associated in any sense with toxic responses in animals.

What you really ought to be focusing on are the other things that can be in the microbial preparation, the other metabolites of the microorganism and the potential for toxins to be associated with the other metabolites within the organism.

So the conclusion that we reached was that the enzyme, itself, is not the issue but really the other things that could accompany the microorganism. So it became a matter of how do you determine the safety of the microorganism so that it can be used as a source of enzymes.

[Slide.]

We considered a number of possible issues including allergies and primary irritations. That, back in 1983, quickly reduced to the idea that there are allergic and irritating reactions that are associated, of course, with enzymes, particularly proteases, but they are limited, certainly in those days, to uses where you would

get into inhalation. So it would be either worker exposure or the potential for their use in detergents and that kind of thing.

We were unable to find any instance where an allergy had been associated with an enzyme that had been used in food processing that had been ingested. To my knowledge, that is still true today. There are, certainly, allergies and irritations that one can have from enzymes but, like I say, those are primarily through worker exposure in manufacturing or they are due to their use within certain specific applications like a detergent. That area has been largely cleaned up due to the reduction of dust generation.

But I would like you all to think about that. If I am wrong, I would sure like to hear about it, but I am unaware of any instance where an enzyme used in food processing has ever caused an allergy.

DR. ATKINS: What about papain?

DR. PARIZA: A papain allergy?

DR. ATKINS: Yes.

DR. PARIZA: To a person ingesting where papain was used?

DR. ATKINS: Or injected into, papain

injected or papain in foods. I thought that was an allergen.

DR. PARIZA: I am not aware of it. I would like to hear more about that.

DR. ATKINS: I just remember reading about sensitivity to papain in the past. It is an enzyme and it is used in food processing as a meat tenderizer.

DR. PARIZA: The question here is whether there is any residual papain to result in an exposure.

DR. ATKINS: That is part of a meat tenderizer. You would sprinkle it on the meat and the meat would be tenderized and it can be sensitized.

DR. PARIZA: I have to admit that I am not familiar with that particular one. But, as far as I know, if that is an enzyme sprinkled on it, that would be one thing. I guess I am thinking particularly of a commercial application where the enzyme has been put in food.

DR. LEHRER: You were saying bacteria, weren't you?

[Multiple conversations.]

DR. BRANDT: I have to remind you, speak

into the microphone. I have already been chewed out once.

DR. METCALFE: The point is the bacterial enzymes that are part of this, that was the primary focus. I should say that, for example, we were aware of people that--there are fungal carbohydrases, for example, there are well-known allergies to that in workers, but we were unable to document that that occurred as a result of people ingesting food that had been treated with those enzymes.

There are reasons for this. The enzymes that are used in food processing are used at low levels and it is generally well less than 1 percent. That would be of the mixture, so the actual enzyme would be much lower than that. The second part of that would be that there is heat processing involved and you guys would know more about that than I would, but, certainly, that would be a factor in all this.

So I think those are considerations but, in terms of the microbial enzymes, I still think that what I said holds. So we did consider that as a factor.

We also looked at the issue of carcinogens

and mutagens, teratogens and reproductive effects. These are certainly effects that are produced by small organic molecules but, so far as we know, proteins are not involved in these effects and there is no product toxicity that you wouldn't pick up as an acute effect due to a protein or an enzyme, particularly an enzyme exposure.

We looked at the issue of antibiotics. Certainly some microorganisms can produce antibiotics. This needs to be part of any screening assay that you are doing. We considered the question of products of enzymatic reactions. Again, I will refer to the original paper but the issue here refers to fairly standard reactions that are occurring as a result of enzymes that would be fairly well known. It is not exotic enzymes doing exotic things to foods.

Interactions between enzymes and other food components was another factor that we looked at as well as the issue of direct effects of enzymes on consumers. Again we are talking about the enzymes that would actually be used in a food-processing setting.

[Slide.]

We developed a decision tree for

determining the safety of enzymes in this original paper. It was aimed at focusing on toxigenic potential, primarily of the source organism. It is important here to consider that you have got bacteria, yeasts and fungi and they all are different and you need to consider them differently when you are thinking about toxigenic potential.

For example, the toxins that bacteria typically produce, the toxins that will produce some type of an adverse reaction upon ingestion, are protein toxins. They are enterotoxins. There are a number that have been described. They will produce a very rapid response as a result of ingestion.

Yeast present, as far as I know, no known problem because they are not known to produce toxins. If you read the microbiology textbooks, they all tell you that yeasts--there are certainly pathogenic yeasts but not toxins associated with yeasts unless, of course, you consider alcohol a toxin.

There is another issue with these that you can get into and that concerns urethane which potentially is carcinogenic, but that is a separate issue. It depends on how the organism is grown.

So that needs to be taken into account when you are dealing with yeast fermentations.

Finally, we get into the filamentous fungi and molds. Here, of course, there is a whole slug of toxins that one could be concerned with, small-molecular-weight toxins, that are potentially carcinogens and mutagens and teratogens and so on. In fact, if you want a life career as a young microbiologist, just go into the mycotoxin area because I don't think you would ever run out of things to do. There is no end to the problems that molds can cause.

Fortunately, there are ways of screening for these. So a lot of the known toxins can be readily screened for in the laboratory so you can get around those problems fairly easily. The other thing is that, by doing the relatively short-term, say a three-month, study, one could easily determine whether there was something in a mold preparation which was, in fact, producing a toxic response in an animal. So subchronic feeding test is very useful for determining the toxigenic potential of a filamentous fungi, of mold.

So the emphasis that we developed was to do specific screening for chemical and biochemical

tests. Of course, in 1983, the ability to do this was nowhere as near as sophisticated as it is today but the idea is to do screening tests with biochemical tests for toxins and to rely on animal tests at the end of the game once you have convinced yourself that there is nothing that ought to stop you earlier. So you are relying primarily on the chemical tests early on to screen out potential bad actors before you get to the animal tests.

[Slide.]

At the end of the day, we reached the conclusion that the enzymes, per se, that are now used or are likely to be used in the future in food processing are inherently nontoxic and that safety evaluation should focus on possible contaminants which could be present.

Assuming good manufacturing practices are followed, toxic contaminants could only come from the enzyme source, itself. In other words, we are assuming that the ingredients one uses ought to be food grade. I think it is very important that the manufacturers use ingredients in enzyme fermentations that are, in fact, safe to begin with and approved by FDA.

So, therefore, you are really talking about toxic contaminants that are coming from the source, from the organism, in this particular case, the microorganisms that are producing the enzymes. So the safety of the source organism should be the primary consideration in determining the safety of the enzyme preparation.

[Slide.]

So that paper was quite well received and particularly the microbiologists liked it. I have had long talks with toxicologists about the ability to be able to do things or think about things in this kind of a manner with regard to determining the safety.

So things went along pretty well until we reached the early 1990s when, by then, it was clear that genetic modification was coming into the fore and so this presented, then, new challenges that needed to be addressed.

If you look at the paper, Biotechnologies in Food: Assuring the Safety of Foods Produced by Genetic Modification, which was published in 1990 produced by the International Food Biotechnology Council, one of the chapters deals with food and food ingredients including enzymes which are

derived from genetically modified organisms. The enzymes was the particular part that I dealt with.

Incidently, that still represents a very, very, very comprehensive list of all the known toxins that are associated with plants, particularly plants, but there are also microbial toxins listed as well, although, in that case, because of the mycotoxins, that part of the list could be updated.

But if you want to see a really comprehensive list of toxins associated with plants, this is an excellent source. There are something like 225 toxins that are associated, that were identified and discussed, at least to some extent in this report and so I would refer you to that as a very nice compilation of things.

[Slide.]

So the new discussion points that we considered in 1990 were information on antibiotic resistance genes, vectors, DNA inserts, DNA from intermediate posts. These were all the things that came into consideration in our 1990 presentation.

[Slide.]

We, basically, at the end of the day reaffirmed the basic concept of the original

decision tree but we added on top of that six new decision-tree questions regarding genetic modification.

[Slide.]

Those are as follows: does the microbe end up in the food? Is the organism free of transferable antibiotic resistance genes? Does a resistance gene code for resistance to a substance used in the control of disease agents in human or veterinary medicine? Are the vectors characterized and free of attributes that would render them unsafe for constructing microorganisms to be used in food-grade products? Does the DNA insert code for a substance that one could consider safe for use in food. Finally, is the microbe free of DNA from some intermediate host which could code for a toxic product.

So these are the new questions that we felt were relevant to the whole issue of using an organism, a microorganism, specifically, as a host for a gene that could then produce a new enzyme that that organism would not have otherwise have produced, would not naturally produce.

So these are the questions, then, that we felt needed to be put on top of the original

decision tree to come to grips with this.

[Slide.]

This is just a rendition of what I just said.

[Slide.]

So the focus of the decision tree is on the safety of the organism and the products it produces. It is assumed, again, that if the organism is nontoxigenic and nonpathogenic, then foods and food ingredients produced from the organism under good manufacturing practices will be safe to consume. That was a conclusion that was reached in 1990.

Now, we have reached 2000. We have reached the new millennium and we have discovered there are yet--or we have put into practice, I should say, yet other ways of modifying enzymes. So now one needs to consider the possibility of engineered enzymes that may vary slightly from their naturally occurring progenitors.

One thing to consider in this case is that the kinds of engineering that one is doing--I will talk about this in a little more detail in a few minutes, but the kind of engineering that one talks about doing is within the variation that one might

normally find. We are not talking about wholesale reconstruction of an enzyme, but usually a change of an amino-acid sequence here or there which would make the enzyme, either increase its activity under some particular condition to increase its resistance to heat and that kind of thing.

So they are relatively small changes. Fortunately, there are very large databases that one can use. I will refer you to the paper. In fact, I think we are going to have copies of it for all of you which will give you, really, a very large compilation of all the databases that are available for being able to consider what kinds of changes are out there naturally, what kinds of things one could potentially do with an enzyme.

The other thing about this new paper that you will find; Table 1 has an enormous listing of enzymes. It goes on for four pages. I thought we had them all but, even with four pages, we missed a couple. But at least you will find most of the enzymes, virtually all the enzymes, anyway that are currently in use or at least were in use as of 2001.

So you can get some feel for the kinds of enzyme products that are used in this case

worldwide.

[Slide.]

Another part of this is that we have also now come to recognize something that wasn't so clear in 1983 and that is that all microorganisms are, to some degree, genetically unstable. So it is important to consider these factors in determining the safety of the producing strain and the products that it produces. This is something that is very important to keep in mind.

[Slide.]

We revamped and expanded the decision tree to fully encompass current industry practice and we worked with the industry, the enzyme-manufacturing industry, to find out what it is that is actually being done because, when I went into this project, I said, we don't want to be talking about things that could be done or might be done or maybe were done last year. We want to know what is being done so that we can evaluate things based on current industry practice, and so that is really where an important focus is here.

As I say, we included an almost complete list of microbial enzymes. In fact, I think it is a complete list of microbial enzymes used in foods.

One enzyme I know we missed was a nonmicrobial enzyme. So, again, we were primarily focused on microbial enzymes.

[Slide.]

Now, this is a very important concept, particularly with what we know about microorganisms today, and that is the safe strain lineage. There are strains that industry, that various enzyme manufacturers, have been using for a long time, producing different products, different enzymes in particular, using a specific strain which is kept in house, which is controlled, which is kept away from contamination.

Those are the strains that one feels most comfortable with. If you go out in the back yard and you dig something up, you might think it looks exactly like the one you have got in the lab but it may not be. And that gets back to this whole issue, again, of genetic stability.

If you want to go through the trouble of sequencing it and showing that it is exactly the same thing that you have in your lab, that's fine, or in the plant, that's fine. But an important consideration in terms of safety evaluation is safe strain lineage.

If you are able to determine that an organism, in fact, doesn't produce toxins, doesn't produce adverse problems that one would be concerned with, then you should be able to use that organism as a starting point, logically, for further modifications. It would make more sense to begin with that than it would be to begin with something that is less characterized and less well-known.

[Slide.]

So this is the decision tree. I won't begin to ask you to go through all this stuff from this, but this just shows you how complicated it gets. But I will go through just a few of the issues.

[Slide.]

Number 12 tells you that is where you will end up if things don't get booted out of this at any point. Number 12 says that and undesirable trait or substance may be present and the test article is not acceptable for food use. If the genetic potential for producing the undesirable trait or substance can be permanently inactivated or deleted, the test article may then be passed through the decision tree again. The test article

in this case would be the enzyme preparation, what you are actually selling, not purified enzyme, per se, unless you are selling a purified enzyme.

DR. ASTWOOD: A quick point of clarification. On Number 11 there, the no-adverse-effect level, is that a subchronic study or an acute study?

DR. PARIZA: It could be either one. A lot of this is based on comparative toxicology. It depends on the organism. It depends on the background of what you are talking about. But I will come to that in a moment.

[Slide.]

This is such a long thing, I thought I would split it up so it is a little more readable for you, but it begins with the question, is the production strain genetically modified. If the answer is yes, you go on. If it is no, you go to 6, and we will come to 6 in a minute.

If it is genetically modified, then you ask question like, is the production stream modified using our rDNA techniques It would be possible to modify an organism without that; for example, through traditional mutagenesis.

Then if you are using recombinant DNA

techniques, then you go on to specific questions relating to recombinant DNA. That is what 3a, b, c, d and e refer to. One of these, you will see, again, refers to a NOAEL, no observable adverse-effect level. Short-term oral studies, we are talking about studies that are designed for the questions being asked.

If you are working with a bacterium and you are worried about the potential for an enterotoxin, then you design your tests in certain ways. If you have organisms that have the potential to produce small molecular-weight toxins--for example, molds--you would design your tests in other ways.

Of course, you first do your chemical or biochemical screening before you even get to this question. But these animal studies are tailored and designed to go after the kinds of issues that could be associated with the particular strain that one is concerned with.

Questions about antibiotic resistance gene, whether those genes are coding for drugs that are related to the treatment of disease in humans or in animals and other introduced DNA and whether or not it is safe for constructing food-grade

organisms.

[Slide.]

Then we go on to the next part of it which just says concerns, if the DNA is randomly integrated into chromosomes, another issue that one needs to consider. Is the production strain sufficiently well-characterized so that one may reasonably conclude that unintended pleiotropic effects--that is another issue that you need to be concerned with. This was first described in plants where one gene can affect a whole bunch of other genes.

That is a very important consideration, particularly with eukaryotes, again in the molds and things. So, again, if you have got a lot of information from safe-strain lineage, it makes it a whole lot easier to do these characterizations. If you are working with brand-new strains, you have to do a lot of work to get to the point where you can be sure that you, in fact, have something that is safe to use.

That is where 6 comes in, safe strain lineage, as previously demonstrated by repeated assessment via a evaluation procedure like this or one that is very similar. If that is the case,

then, at that point, you couldn't separate it.

If there are still questions, then you need to go on and ask, for example, is the organism nonpathogenic. Is the test article free of antibiotics. I know a lot of screens that one could potentially do. Is the test article free or oral toxins known to be produced by other members of the same species? Are the amounts of such toxins in the test article below levels of concern?

Then, the one that you asked me for which is about the no-observable adverse-effect level. There are a number of different tests, animal tests, that we describe in here that are aimed at going after the kinds of issues that might be associated with the organism, source of organism, that one is concerned with.

Again, I will refer you to the paper. I think you all be getting copies so you can look at this in depth regarding that.

[Slide.]

These are the issues that I think address the toxicology, what I would call or what Dr. Metcalfe referred to before, as the traditional toxicology questions. Of course, we don't have worked into this some kind of a test for

allergenicity, per se.

It is really up to you to come to grips with the whole issue--that is what you are doing here today--the whole issue of allergenicity. I am not going to pretend to have any answers for you, per se, but there are some considerations that I think you need to keep in mind when you are dealing with enzymes used in food processing.

One is the low level, the control level, that one can use in this particular case and that compared certainly to other proteins that are present the levels are quite low. The second issue is, of course, that the food almost always go through some heat processing step which would likely certainly inactivate the enzyme, would likely denature other proteins that are in there, too, to some extent.

The other important question is the whole idea of safe strain lineage because, generally, at least the kinds of enzymes that traditional manufacturers are going to produce today to build a food, are going to be enzymes that are coming from organisms that they have used over the years and they have made modifications here and there to improve enzyme yield, or they might not be

engineering those enzymes to--making very small modifications to increase the ability of the enzyme to tolerate heat, and that sort of thing, maybe change some of the substrate specificity.

Again, the changes that are being made are very conservative and within the range of what one would find in nature. That is an important consideration. It is certainly an important set of questions to ask and that is what this is all about.

So, I don't think the allergenic potential for food-processing enzymes should be a real top priority for you compared to some of the other things you have heard about today.

So, at that point, I will stop and ask for questions.

DR. BRANDT: Questions?

Questions of Clarification

DR. BUCHANAN: Yes; I have a question. Bob Buchanan. Approximately how many enzymes have been added to food and none of which has yet been shown to cause an allergy?

DR. PARIZA: The only exception I can think of is the papain story. I guess the issue is whether it is really the papain or something else

that might be in there. With that exception, and I have to admit I am embarrassed and I should know more about it.

In terms of microbial enzymes, you are talking--well, you can look at the list. I didn't count them, but I am going to say there are certainly well more than 100 here. You will have this paper very soon. There are many, many, and there have been more added in the last ten years. But they are generally from the same organisms. These are new enzymes that are being used but there is not a big change in the strains.

DR. BUCHANAN: Even so, they are different proteins.

DR. PARIZA: Yes. That is another important consideration. People think that, because they call an enzyme by a certain name, that if the enzyme comes from another organism it is the same enzyme. That is not true. We know that. The protein structure can certainly change.

DR. BRANDT: Other questions? Thank you very much.

We need Dr. Maryanski.

DR. LANE: If I am guessing right, he is scrambling from the auditorium to here. He wanted

to see how the presentation was coming in.

DR. MARYANSKI: I just spent a little time in the hinterlands, meaning the auditorium. I would suggest that we do try to speak into the microphones and one person at a time. It is difficult for the people in the auditorium to hear otherwise.

So I will try to use a louder voice and hope it holds up.

DR. BRANDT: I just want to remind everybody that I have now been sensitized. So, the next time you don't use the microphone, I am going to have an anaphylactic--please use the microphone.

FDA Food Biotechnology Policy and Current Approaches to Allergenicity

DR. MARYANSKI: Thank you very much, Mr. Chairman. Good afternoon, ladies and gentlemen. Again, on behalf of all of us who have worked and put this meeting together, we really appreciate all of you taking the time from everything else that is very important to you to come and help us out with this. We look forward to working with you over the next couple of years, actually, hopefully.

This is a first meeting. We want to provide you with enough background so that you have

a good sense of how we have got to where we are today. So part of my presentation is going to be quite old information for a number of you, but we thought it was important to give you a sense of what our policy is, the point we have reached today and why we are where we are.

Then I will also give you some information about what our current policy is. So this is all, again, by way of giving you some background information so that you will have that as you being your discussions.

[Slide.]

The Food, Drug and Cosmetic Act, as I think you have probably understood by now, is the statutory authority, the legal basis under which we work and that really guides everything that we do in the sense of what we can do and what we cannot do.

The Act is very broad. I won't go into all of its provisions but it has basically been in place in essentially its current form since 1938. So it has been around a long time. It has been amended many times, as you heard earlier, in 1958, to give us authority to approve the food additives. But the Act is very broad. It gives us both

authority over the safety of foods and sets the standards for those foods. It also gives us enforcement action, to take action if anyone or any product violates the Act.

We base our policies and our regulations on the best science that we have at the time. That is one of the reasons that we are all here today, to examine what the science is in a particular area.

Our authority is about products that are in interstate commerce and products, that means products that are imported into the United States, products that are moving within the United States.

We do not regulate research. I think that is an important point but it is also important to understand that developers tend to come in and see us early in the process and we encourage them to do that. So we have a number of interactions at the research level, but we do not have authority to regulate research in the development of food, food ingredients.

Of course, our mission is to ensure a safe and wholesome food supply. I think I will emphasize the fact that, while we talk about biotechnology a lot and I, in particular, talk

about it a lot, we are not proponents of the technology or the products. Our role is protecting public health. So that is our mission.

[Slide.]

You have already heard about this. I am going to go through this very quickly now, but just to give you a sense of what our authority covers. There are three agencies, federal agencies, that are primarily responsible for the safety of food produced by biotechnology, FDA, EPA and USDA.

We, of course, are responsible for most foods. Meat, poultry and certain egg products are regulated by the Department of Agriculture and USDA. FDA regulates everything else in the grocery store, so all the other packaged foods, all the fruits and vegetables, all fall under FDA's authority. So, in terms of crops, the foods derived from crops all fall under FDA's authority.

USDA, in terms of products produced by modern biotechnology, is primarily responsible for ensuring that those crops are not plant pests and that those products can move into the country as plant products. So their oversight takes into account most of the environmental issues that might be thought about for these products.

So, as you heard earlier, we defer to USDA on most environmental issues. The growing of crops, you might think of as primarily being under USDA and the safety of those foods, feeds, derived from those crops is FDA.

[Slide.]

EPA has authority to regulate pesticides under both FIFRA, which is the Federal Insecticide Fungicide Rodenticide Act but, also, under the Food Drug and Cosmetic Act. EPA sets tolerances for safe levels of pesticides or exemptions from tolerances including tolerances and exemptions under the Food Drug and Cosmetic Act for pesticides and foods.

So, if you think of biotechnology corn, for example, where it is a BT corn, you have the BT as a pesticide trait. It is a characteristic that has pesticide properties. So that trait, the BT, falls under EPA. They do the safety assessment of BT.

USDA has authority over the growing of that crop during the field testing and the exception from their regulations for commercial growing. FDA has authority over the corn products that would be used, say, as high-fructose corn

syrup or animal feed that are derived from those corn plants. So, in the case of a BT corn plant, all three agencies have some authority over that product.

[Slide.]

In 1992, we published what we call a policy statement. This was our attempt to answer questions that were coming to us early in the development of crops produced by modern biotechnology. Companies were at the point where it was obvious they were going to eventually want to market foods derived from these crops. They knew this was a new technology and so they were asking us questions about what would be the legal basis for how these foods would be regulated and what would be the safety testing that would be needed to ensure that these products were safe for the public.

The '92 policy, which is available on our website, was our effort to answer those questions. We set out the legal basis for how we regulate foods. We explained the various provisions of the Act that apply to regulating foods and food ingredients but, more importantly, we set out the issues that we thought should be taken into account

for safety of these products.

We did that through both text and a series of decision trees that explain what the issues are. We do not describe specific tests. We simply indicated what kinds of questions should be asked. That was done so that developers would have the advantage of our guidance early in the process before the products came to market.

This policy statement covered fruits, vegetables and grains, basically foods that are derived from crops, and it applied to all methods of plant breeding. We did this for the purpose of answering questions about modern biotechnology--that is, the use of recombinant DNA techniques, but we thought that these products should meet the same standards that apply to all other foods.

If a food is derived by conventional hybridization, or embryo rescue, or some clonal selection or recombinant DNA, those foods should all meet the same standards under the Act. So the '92 policy really is about all foods derived from crops but intended to answer the questions about the use of rDNA.

When I speak of foods, unless I specifically mention feeds, I am also speaking of

feeds. Feeds are included in our definition, our legal definition, of food. So the policy does apply to both foods and feeds.

[Slide.]

I am going to give you a little bit of a sense of just what are the very broad-brush legal tools that we have to ensure the safety of foods. There really are two provisions. Foods, under the Act, are not subject to a requirement for review or notification or an approval by FDA before they are placed on the market.

The first time kiwi, for example, was introduced into U.S. grocery stores, no one was legally required to tell FDA about that. On the other hand, the Act does set out the safety standards for foods so the developer, or the sponsor who is putting that product on the market, has a legal duty, under the law, to ensure that that food is safe.

FDA has enforcement authority to take action if that product is not safe. If that product violates the law in some way, then we have the authority to take action to prevent that product from continuing in the marketplace. We even have authority, under some circumstances, to

initiate criminal prosecution if someone breaks the law.

So the system works for foods in the sense that a developer does not want to put a product on the market that would be called into question in terms of its legal status or that FDA would raise questions about. A company who is buying a product wants to make sure that any product they buy from a developer meets all the provisions of the Act so they will ask, is this okay with FDA. So that is built into the system and it is why this system works effectively.

We do have premarket authority for food additives, as you heard Dr. Rulis mention earlier. In 1958, we were given authority and the requirement to assure that any substances that were added to food or were intended to become components of food did undergo premarket review and approval and the issuance of a regulation by FDA before they were used in food, but there is, as you heard, an exemption for those substances that are generally recognized as safe.

Of course, there are many substances that are in the marketplace under that exemption. Things like salt and vinegar and pepper and other

common things added to food were generally thought to be generally recognized as safe. Congress provided a mechanism for newer substances to be considered safe if there was this wide recognition among experts that the substance was safe for use in food.

Just to show you how we have applied this to bioengineered foods, we have said that, if a gene is introduced into a crop plant and that gene then results in a protein, for example, or some other substance that is new to the food, that substance will be treated as a food additive if there is not a basis to consider it generally recognized as safe.

So this is our legal tool to be sure that, if there is any modification of the food that introduces a substance that, in fact, should be reviewed as a food additive, we have that authority to do so.

What we have seen to date have been mostly, almost entirely, metabolic enzymes that are very similar to enzymes that are components of food already. So we have only used the food-additive authority one time, at this point, and that was at the request of Calgene when they were developing

the Flavr Savr tomato, which was the first product we were asked to review. They wanted to be sure that that product was shown to meet the highest standard it could meet under the Food Drug and Cosmetic Act.

So they actually asked us to regulate that kanamycin-resistant enzyme in the tomato as a food additive. So we did not regulate the tomato as a food additive, but that one substance which was the only new substance in that tomato. So there is a food-additive regulation for the enzyme that is produced by the kanamycin-resistance marker gene.

But, to date, we have seen a very narrow class. That is one of the things you will probably hear from us several times over the next couple of days is that, at this point, we are looking at a very narrow range of the possible proteins that we might be dealing with. I think that is an important consideration.

We did issue, as I said, guidance to the industry. That basically gave them a yardstick to know if they were meeting the expectations that we would have for safety testing. We recommended that companies come in and consult with us. We said this is new technology. It is important that we

know about these products before they go to market even though there is not a legal requirement for companies to come in.

Our experience has been that, as far as we know, and as far as anyone has been able to report to us, all the products that have gone to the market in the U.S. have been through FDA's consultation process before they have gone to market. We also, in the '92 policy, laid out our preliminary thinking on the labeling of products. I won't say much about that except to say that any characteristics that are new to the product, that make that product substantially different, would be required to be labeled to disclose that difference.

So, if there is a new allergen in the food, that would have to be disclosed in the labeling. If there is a nutritional difference that is different from what the consumers expect, then that would have to be labeled. The consumer has to know how to cook the food or prepare the food in some different way. That information would have to be labeled.

[Slide.]

We did establish, as I have said, a basis for companies to come in and talk to us. We really

started out wanting to make sure that we were operating, treating everyone internally, by some standards. So we developed some internal operating procedures which really became our consultation procedures. We made those public so that everyone would know how we were operating.

Those were put out in 1996. They were based on the experience that we had had up to that point in developing our 1992 policy, the evaluation that we did on the Flavr Savr tomato and other of the first products that came to market shortly after our first decision in 1994.

We had some meetings of our Food Advisory Committee in 1994 where we discussed our policy and our scientific approach with the committee and we used the Flavr Savr tomato and other products as examples of products that were evaluated under the approach we had put out. At that time, the committee felt that, for the types of products we were seeing at the time, that that was a reasonable scientific approach for assuring that these products would be as safe as other foods on the market.

One thing that we have always encouraged developers is to come to see us early and often.

That is very important when products are new. We don't expect them to come in on products that we know, that we are very familiar with, and they are familiar with what needs to be done to assure that they meet all the provisions of the Act. But when something is a new product, has new traits, new characteristics, then it is important that they come in very early in the process so that our scientists can have a dialogue with their scientists about the issues that need to be examined and the appropriate tests that would be carried out.

[Slide.]

I want to give you just some general ideas about some of the issues we have thought about in developing our guidance to industry on safety testing. If you think about it was about 1989 when Calgene started to ask questions about the Flavr Savr tomato and other companies were also coming in at that time.

We realized that they were asking us a question we really hadn't been asked before. We are very used to dealing with food additives and other ingredients that are added to food. But we were being asked about a whole food. As I told

you, there is no requirement for new varieties of corn and soybeans and potatoes to come to FDA before they go to market.

But now companies were saying to us, we have a new tomato, for example. We want to know what kind of testing will show that it is safe for people to eat. That was really a new question for us in the late '80s. So we had to decide how to go about that.

We weren't the only ones. This was being discussed in the international community as well. But one of the things that we decided, after looking at the kinds of products, was that these were basic food crops, fundamentally. They had been modified using recombinant DNA techniques to introduce new traits into those crops, but, basically, it was still corn, potatoes, soybeans, and so forth.

So we weren't really dealing with an entire new entity. We were dealing with new crops with new traits. So we thought that the best way to approach that would be to compare the new variety with its traditional counterpart. This was for the purpose of identifying, first of all, what is different about the new product compared to what

has gone on before it, so that we can make sure that any differences that have been introduced are safe, and then, secondly, to make sure that the food still is what you would expect it to be for that particular crop.

This required a different approach. For food additives, we were very used to characterizing the additive and using a series of toxicological tests to establish its safety. But it was obvious from other things we had learned, from protein supplements and other complex mixtures, that a substance such as a tomato or a potato or corn that is, in fact, a complex mixture of chemicals, would not work as well in the traditional kinds of toxicological battery of testing.

So we worked out a different approach that takes into account several different kinds of information. The first is really the screen that plant breeders do all time with new varieties. Plant breeders look at the agronomic characteristics, the growth of the plant, the setting of seeds, flowering of the plant, the yield from the plant, how it grows in different regions. That is the first screen and that still occurs with products produced by modern biotechnology just as

it does with conventional varieties.

That is one of the mechanisms that developers have to screen out the so-called unintended effects. They occur by all methods of plant breeding.

But we also have new tools in terms of molecular analysis now. We know much more about the traits that are being introduced into the plant. We know what the gene is. We know the function of that gene. So we can focus safety assessment on the new characteristics of the plant based on what that substance is.

We also, then, look at other aspects of the food. Has it been changed in any ways with respect to nutrition. Does it still have the same vitamins, the same minerals, the same components of the plant in terms of toxins, antinutrients or nutrients that are expected for that crop. Each crop, of course, is different.

It is taking all of this information into account that gives us a picture of is this product safe in terms of the changes that have been made in the product as well as is this food still basically the same food in addition to those changes.

We do not run, normally, toxicological

tests because of the difficulties of testing whole foods. But, nevertheless, if this information does not resolve all of the questions, then one could design an animal test, for example, to answer a specific question.

That is sort of, in a nutshell, the basis of safety assessment.

[Slide.]

But, just to give you a sense, while I say we don't generally do toxicological testing, that is not to say that we would never do it. In fact, there would be circumstances where we would. If there is a really new substance in the food that we don't have any knowledge about its ability to be consumed safely, then that substance would need to be subjected to the more traditional kinds of toxicological tests. We haven't run into any of those, so far.

[Slide.]

This is just to give you a sense of some of the major elements of the safety assessment and, again, to emphasize that what we are looking at is both the intended change in the plant--that is, are there new substances that will be in the food and, if so, what are they, what is their structure and

function, and do they come from a source that would create questions about allergenicity.

This is really where we are focusing much of our discussion these two days; can we digest this substance. Is it consumed normally and how much do we eat. These are standard food-safety questions. There is nothing exotic about these questions for bioengineered plants. They are the same questions we would ask for a non-bioengineered plant.

But we also take into account unintended modifications because we know that unintended changes occur by all methods of plant breeding. As I have said, it is something breeders have to deal with normally.

So, in addition to the screen that breeders usually do, we also have the ability now to make sure that the genetic material is stably incorporated. This is one way of making sure that changes don't continue to occur in successive generations.

We also expect companies to look at the composition for these nutrients and toxicants to make sure that, basically, the food is what we expect it to be. This is another way of monitoring

for changes that would have occurred in the food in addition to all of those things that the developer looks at in terms of how the plant grows in the field.

So it is taking into account all of this information, then, that gives us a sense of whether this food is as safe as other foods that are on the market. That is just to emphasize the fact that the developers have the first stage. That is just an example of just a few of the characteristics that are examined for soybeans, in terms of their agronomic characteristics.

[Slide.]

This is a slide to really emphasize--we talk about consultations and we have often said that companies submit a summary of data to us as part of these consultations. I just have two quick slides here to show you that this is not a postcard to FDA. When we say that companies are providing us information about their safety review, we do not ask them for all the raw data. But we do ask them for enough data to show what kind of issues they have addressed, what kinds of tests they have done and what the results are that they have found.

[Slide.]

These are just examples. So a submission on a consultation will be, say, 100 to 200 pages, just in round numbers. So we are not talking about a letter to FDA saying, "I am going to market with this product." This is the culmination of discussions with our scientists about the testing on these products.

[Slide.]

This is just to give you a sense of the fact that there are a number of major crops that have been developed by recombinant DNA. We have beet, canola, corn, cotton, potato, soybeans, flax, radicchio, squash and tomato. So there are about ten crops there, but some of them are very major crops. So the techniques are being used to a limited basis in terms of the breadth of the food supply but some of these are very major components of foods.

And the number of traits is also relatively limited at this point. There are many products that are resistant to various pests and disease as well as tolerant to chemical herbicides. We have several products that are modified--vegetable oils--but most of them are, at this point, for agronomic traits.

So, in terms of how we look at these, and there was a question raised this morning about reasonable certainty of no harm, we are looking at the safety of a food here. The standard that we expect developers to meet is to show that the new food is, in fact, as safe as other foods on the market.

So it is a little bit different standard than for the specific food additive. This is not a comprehensive review where we look at all of the data and we establish an administrative record for that data and a regulation which is the process for food additives.

This is a process that is one where we satisfy ourselves and our scientists that the company has addressed all the scientific questions. We reach a point where we are satisfied that there is no scientific issue related to the safety of the food for human consumption that has been left unresolved.

[Slide.]

In 1999, we conducted some public meetings. This is a picture of an exciting meeting we held in Oakland, California. We held three meetings and the purpose of these meetings was to

listen to the public. At that time, we were getting an increase in the number of questions about these products from the public and we also wanted to have an opportunity to explain to the public what we were doing, what our policy had been up to that point.

But we really needed to hear what the basis was for the concerns that were being expressed. At these public meetings, we had panels in the morning and afternoon, one on scientific issues, one on public-information issues, including labeling.

There were a number of panelists and speakers. We had the panelists and, of course, we had public speakers at each of these meetings. We had written comments submitted. This was a very important process.

One of the things that we learned from the public meetings is that there was no information presented to us that would question the safety of products that had been through FDA's consultation process. There was a lot of concern about the fact that that process was a voluntary one in the sense that companies were not required to come to FDA for these consultations. That was something that the

public was really not comfortable with.

Now, the Food Drug and Cosmetic Act is not voluntary. I think it is important to understand that. But it is voluntary for companies to actually come in and consult with us. Calgene could have put the Flavr Savr tomato on the market at any point they had decided to do that, except for the fact that they had asked for a food-additive regulation for the enzyme. But, basically, the point is that they were not legally compelled to come to us. But that is something the public was not comfortable with.

So, as probably most of you know, we have proposed to make the current consultation process mandatory, to require companies to notify us 120 days prior to marketing. We would still continue our normal consultation process but the final step of actually submitting the information about their safety assessment to us would become mandatory.

We heard some other things, too, from the public meetings. One of the things we heard was that there may be products in the future that will be more complex than we have had up to now. We, of course, are aware that the science is advancing.

One of the messages that we got from our

earlier 1994 food advisory committees where we looked at Flavr Savr tomato and other products was that the committee members, after hearing about all the data that had been developed on the Flavr Savr tomato said to us, this is very interesting, it was very good exercise for the first product.

They thought that FDA and the industry did a very good job in terms of all the scientific tests and the evaluation of those tests. But they also recognized that, in fact, that product did not raise any substantial public-health issues and they actually suggested to FDA that, for products that were similar in nature, that we might want to have a more abbreviated process.

That was the genesis of our consultation process because we agreed, based on the types of products we were seeing, that this consultation would be an appropriate level of oversight given the kinds of products we were seeing, always with the recognition that, if a product had different characteristics that raised particular scientific issues, that it should undergo an appropriate level of review.

But, from the information we heard at the public meetings, we realized that it is important

that we take steps to keep up with the science. The forming of this subcommittee is one of those steps. We have this committee established so that we can bring to this subcommittee questions about the science that we are dealing with at the time.

By having the committee established, that gives us an easier mechanism to do that on a more routine basis.

A question?

DR. ATKINS: Dan Atkins. I have a question. Is 120 days adequate? Maybe in this environment, where there are fewer applications, but what if there are more? Can you keep up with the load if that increases, et cetera?

DR. MARYANSKI: Yes. And that is something that we have thought about. Based on our best projections in terms of what we expect development to be, we do think that 120 days is probably going to be an appropriate time frame.

This is a proposal. It is open for comments. I should say that we have received something over 100,000 comments. We have now distilled those comments down, so we are actually beginning to review the comments. But that is one of the issues that we will be looking at in terms

of moving toward a final rule on this.

DR. BUSTA: Frank Busta. Earlier you indicated that any kind of new variety is assessed in the same fashion. If there is a new variety of barley or wheat, that you would run--that any variety, generated in any way, would be evaluated by FDA.

DR. MARYANSKI: No. Our '92 policy does cover all new varieties of plants in the sense that we set out what the legal standard is and what we would think the questions we be about safety. What we have said is we want companies to consult with us on the specific use of the new technologies. So we do not have companies coming in to talk to us about varieties that are developed with conventional techniques.

What we are saying is they have to meet the same legal standards under the Act in terms of the foods that are placed on the market. But we are only asking companies to come to us who are using the newer techniques. We have had, in fact, once or twice, companies come to us and say, "I haven't used recombinant-DNA techniques but I have a question about a new variety," and we can do the same kind of consultation.

DR. BUSTA: This is only for bioengineered foods and not the other?

DR. MARYANSKI: The actual consultation process is set up for bioengineered foods. The reason for that is because they all raise a similar set of questions. We wanted to establish this process so that the companies--we would treat everybody the same.

Yes?

DR. LEHRER: Sam Lehrer. I have a question about the notification in terms of the process, itself. The notification occurs and then what happens after that?

DR. MARYANSKI: There are two steps to the process in a broad sense. The first step is the early consultations where we have a scientific dialogue between our scientists and the company scientists in terms of design of tests and so forth. At the point where the company believes that they have done all of the testing that needs to be done to market a safe product, we ask them to submit that information to us, information that explains what they have done, not all of the data but information that is sufficient to give our scientists a sense of what they have actually

found.

Once we have reviewed that and we are satisfied that we have no further questions, we send them a letter that says essentially that, that, based on what you have told us about this product, the testing that you have done, we have no further questions.

As you may have had Dr. Rulis say this morning, our letter also says--we remind them that it is their continuing responsibility to ensure that that product meets the provisions of the law. So, on other words, the burden is always on the developer for a food to ensure that that product is safe and wholesome.

Our review gives us the comfort that they have done all the things that we think should be done before that product goes to market. So this is a different kind of process than a food-additive review process.

DR. LEHRER: You also have the option of not agreeing?

DR. MARYANSKI: Yes; we do not issue that letter until we are satisfied that all the questions have been addressed.

Now, this morning you heard about eighty

consultations and fifty that have been final. Just to give you a little clarification, some of those are recent submissions that we are just beginning to review. Some of them are very old, products that companies have probably given up on and will never complete for various reasons.

DR. BRANDT: Are you through? Or do you have other--

DR. MARYANSKI: I have just a couple of slides on our allergenicity approach.

DR. BRANDT: Fire away.

DR. MARYANSKI: Okay.

[Slide.]

Now I want to just give you an overview of the approach that we have been using to assess the likelihood that a new protein would be an allergen; in other words, to make sure that we are not introducing any new allergens into foods. I think you have heard that virtually all allergens are proteins. On the other hand, there are thousands of proteins that make up the food supply and, at least as far as we know, only a small percentage of proteins are found to be allergens.

In terms of the use of recombinant-DNA techniques, that means transferring genetic

material from one source--it can be any source, plant, animal, microorganism--to a food crop. That genetic material often results in the production of a new protein that may even be present in the finished food--not in all cases, but in a number of cases.

So the question is will these proteins be allergens. That is really what we are here to talk about over the next couple of days.

[Slide.]

We have been talking about this for a long time, as you can see from this slide, and we expect to be talking about it for a good bit longer.

Just to remind you again, in terms of developing our draft guidance, we see this as the beginning of that process. And so we are looking for your initial thoughts on this and we will be back to talk to you more about this.

But, in our 1992 policy statement, we recognized that this was a very important component issue for safety assessment. What we said at that time was we thought about the fact, as Dr. Metcalfe said earlier, there are certain foods that are commonly allergenic such as fish and milk and soybeans and so forth.

We thought that, well, if someone removes genetic material from that source, they could remove material that would encode for an allergen. Now, obviously, there are many genes in that plant and there are many genes that will not be an allergen, even in a plant that is known to produce allergic reactions, but we thought that our first approach should be to assume that, in fact, an allergen has been transferred for something that is commonly allergenic unless the scientific information can demonstrate otherwise.

This is to make sure that there is not really going to be an allergen that we know would create a serious reaction from something like peanut, for example, transferred into another food crop. Our sense is that no one is going to transfer any genetic material from a crop such as peanut because we know about the seriousness of those reactions.

But we knew about genetic material based on the source of the gene in terms of if that source was a material that produces allergic reactions. We knew that was a concern in 1992. The harder question at that time was, well, what about most of the genes we are seeing in

bioengineered foods which really don't come from these sources. We didn't have any that come from those sources. They come from bacterial sources or plants that are not food sources.

So, at that time, we simply asked for comments. We didn't get very many. But we did do some other steps to make sure that we were addressing this based on the best science that we had at the time. The three agencies convened a scientific conference that was held in Annapolis when we convened a group of food allergists from around the world, actually. We looked at this issue and they gave us some suggestions about how to deal with it.

We also discussed this approach with our Food Advisory Committee back in 1994 in terms of establishing our policy and our evaluation of the first products that had gone through the system.

[Slide.]

So the approach that we are using today was established back in about 1994. That approach involves comparing a new protein with proteins that are known to be food allergens to make sure that a protein that is now introduced into a food crop does not have any of the characteristics that are

known for food allergens. That involves, of course, looking at the source of protein to be sure that it doesn't come from a source that is known to produce food-allergy reactions and also looking at its sequence to be sure that it is not similar in its sequence, both in terms of its overall sequence and in terms of what they call epitopes which are the regions that may be binding to IgE and protein, to make sure that there are no known matches to the protein and to look to see if that protein is readily degraded by acid, by digestive conditions and so forth.

That, as you have heard, is not a definitive test. But proteins that are readily digestible, for the most part, usually are not food allergens. In the area of allergenicity, as you may have already gotten a sense, there is an exception to everything that one might put forward as a general principle. So you always have to keep that in mind.

But the idea here was that, in taking into account a number of different kinds of information, altogether, that that would basically give us more confidence that this protein is not likely to be an allergen.

What the experts said to us is that, in terms of these proteins derived from bacteria, we can't say that a protein will never be an allergen. But they didn't expect that most proteins would be and so they felt that this was the best scientific approach that we had at this time.

Obviously, if the protein is derived from a source that we know to be allergenic, then there is a different approach and there is a sound scientific approach that can be used using sera from patients that are sensitive to that particular source.

[Slide.]

In fact, I will start at the bottom with the example. We had a product that was developed and it was a soybean in which a gene from Brazil nut was introduced. It was a gene for the 2SL human protein which is a gene that confers a storage-protein characteristic to make a storage protein in Brazil nut.

We know that certain individuals are allergic to Brazil nut. Steve Taylor's group at the University of Nebraska looked at this product that was developed by Pioneer Hybrid and they found that, in fact, the protein in soybean, this Brazil-nut

protein in soybean did cross-react and, in fact, listed its skin reactions in individuals who were allergic to Brazil nut. That product was discontinued. It never went to market, never made anyone sick.

To date, we have had about 50 products, different varieties of crops, that companies have completed food-safety consultations with us since this approach was put into place. There are about eighteen new proteins in those crops that we have looked at so far.

All of these proteins lack any similarity to known allergens. They are also all readily degraded. Remember that FDA deals with the nonpesticidal substances, that we are not looking at the BT proteins. We have always thought we have all the easy things because at least we know of any toxicity to the substances that we are dealing with up front.

But, actually, seriously, to date, the proteins that have been engineered in the plants are almost all metabolic enzymes, so they are enzymes involved in the ethylene pathway, for example, or they affect the amino-acid synthesis pathway and, therefore, are used for herbicide

tolerance. But they are basically common enzymes in the food, is the point.

We have seen a very narrow class of proteins. What we are going to be asking you to think about is that the draft guidance that we prepare will be based on the kinds of proteins that we have seen. There will be other proteins in the future that will raise different issues, but, right now, we want to focus on what we are experiencing and we will deal with the things in the future that raise different issues because we don't know what those are so we don't know how we would deal with those.

So this is, I think, a very important point to keep in mind for you to think about.

[Slide.]

This has been discussed not just here at FDA, by any means. We have been working with international groups. Others have looked at this as well. The industry, through the International Life Sciences Institute and the International Food Biotechnology Council, published a very comprehensive paper on assessment of allergenicity in bioengineered foods in 1996. So there have been a number of activities.

More recently, the international community has looked at this issue, and you are going to hear more about this very briefly now, but what has happened in that the experience that has been gained and all of the discussions have really crystallized to a point of at least, now, we believe there is a general consensus on an approach for the kinds of products we are seeing today. That is reflected in what are now the international guidelines in the Codex and, since probably some of you might say, what it the world is Codex, I have a slide to answer that question.

[Slide.]

The Codex Alimentarius Committee is a body that was established under the U.S. system by the World Health Organism, WHO, and the Food and Agriculture Organism, FAO, in 1962. It was established to guide and promote the elaboration and establishment of definitions and requirements for food and to assist in their harmonization and, in doing so, to facilitate trade.

What is important about this is that now, under the GATT agreement and the World Trade Organization being established, the Codex is recognized as the international body for setting

standards and guidelines for food safety. So the guidelines that are established under Codex are particularly important.

The Codex is made up of about 165 member countries from all around the world. The voting members of Codex are all government representatives. There are also non-government organizations, both industry and public-interest groups, who are observers of the Codex process and participate in the process, but the voting is all done by the member countries.

One of the things that I am going to tell is our bottom line, at the moment, for you think about and you may disagree, of course--that is why we have asked you to think about it--but it is our feeling from the experience we have had and the discussions we have had in the international community that what you are going to hear about, as the current guidelines that have been developed internationally are something that we want to consider very seriously in developing our draft guidance.

We think that it is very consistent with the approach that we have used to date for the kinds of products that we are seeing. So we think

that it deserves serious consideration and we are very happy to have an expert to tell you about that process.

DR. BRANDT: Questions?

Questions of Clarification

DR. GURIAN-SHERMAN: Doug Gurian-Sherman. I have a couple of questions. Why don't I start with two of them. I don't want to keep beating a dead horse, and I don't think it is quite dead yet, on a reasonable-certainty-of-no-harm issue, the reason I bring it up is because I think the level of oversight that you intend or will give these products has some influence on the level of scientific rigor that goes behind it. So I think it is a relevant issue.

I think it was Bob Lake mentioned earlier that you want harmonization as much as possible between agencies which I think makes sense. My understanding--maybe I am wrong and you can correct me if I am, EPA, when they are looking at allergenicity, which is a similar issue when you are looking at allergenicity for a given protein, say, cryoprotein, I think the standard is reasonable certainty of no harm.

I understand what you are saying in terms

of the whole food being "as safe as," but when you are talking about the protein, itself, it you want harmonization, it seems like the standard would be reasonable certainty of no harm for allergenicity or toxicity or whatever of the protein, itself.

That is one issue. The other question I have is, on enforcement, and, again, think this is relevant because I think it would have implications for what we would recommend should be done up front in assessing the proteins as opposed to afterwards. My understanding is that the burden of proof would be on FDA.

If there was some alleged adverse effect of the genetically engineered food that went on the marketplace, FDA would have to show that there was an adverse effect under the notification process if it was shown to be GRAS as opposed to, just in contrast, if it went through the food-additive process. Then it was be automatically considered adulterated if there was a problem.

Maybe you could just address those issues.

DR. MARYANSKI: Mr. Lake, you need to come up here. First of all, before I turn the mike over to my boss, I don't believe there will be any difference. We don't anticipate any difference in

the safety review of the proteins in terms of allergenicity and we are working very closely with EPA because, basically, they are looking at protein safety for the pesticide products including allergenicity and we are doing the same thing for the nonpesticide proteins.

So, in terms of the science that would underpin the decision, we don't see that there will be any difference.

MR. LAKE: Let me address your other question because it is important. Again, though, before I do that, let me emphasize the point that Jim just made which is, from the standpoint of science, we are absolutely trying to look at this the same way.

The issue you are raising is really a legal issue. I don't represent our chief counsel's office, but let me give a crack at this because I am not only familiar with what we do but have had a lot of interaction with EPA over the years.

Going back to the discussion we had earlier, the law has a very rigorous system in place for those things that are defined as food additives. But it also has a major exemption for things that are generally recognized as safe. The

prevailing view is that those things that are relatively minor modifications of existing foods are in the GRAS category rather than the food-additive category. We have had lots of discussions with our lawyers about that and I don't want to rehash all of that.

But, the things we are talking about, that we have been looking at, all fit within the GRAS box. There is certainly the potential in the future for seeing many things that are in the food-additive box. It is in the food-additive box that the reasonable-certainty-of-no-harm standard applies.

So, for things that got into that box, they would be evaluated the same way we would evaluate any other food additive including using the reasonable-certainty-of-no-harm standard.

The difference with EPA is sort of as follows. Again, I am oversimplifying something that is actually a lot more complex, but when the pesticide law that EPA administers was amended in 1996 by the Food Quality Protection Act, prior to that time, they also had a GRAS exemption for pesticides.

Congress chose, in 1996, when amending the

pesticide law, to do away with the GRAS exemptions for pesticides. So all of the pesticides that EPA would look at, whether they are chemical or bioengineered, whatever, have to go through the standard that is set forth for pesticides.

It actually happens to be in our Act, or the Act that we think of as ours, the Food, Drug and Cosmetic Act, but it is Section 408 of that Act whereas food additives are in 409. So there is a difference in the Food, Drug and Cosmetic Act whereas GRAS standard exists still, as it always has, under 409 for food additives or things that are exempt from that.

But, with regard to pesticides, that exemption was done away with and also the Congress chose, at that time, to take the reasonable-certainty-of-no-harm standard which had been in place for food additives for a long, long time and to explicitly apply it to pesticides really for the first time beginning in 1996.

So now when EPA evaluates a pesticide, they are using all of the criteria that were added by the Food Quality Protection Act of 1996. In contrast, when we are looking at these things, we are looking at the state of the law as it was in

1958.

Now, I understand that people can make a policy argument that maybe the food-additive law or some special law ought to be passed by Congress to deal with bioengineered foods as better looked at by FDA. But that is not our issue for this meeting and not a question that we can resolve in any event.

So what I would come again to Dr. Maryanski's point. I think the focus that we would like this group to take is on the scientific aspect of this, not on the legal or legislative component of it, and give us the best advice that you can give us in terms of the science.

We very much, of course, want to be consistent with our colleagues at EPA on that and, indeed, have a very strong desire to have as much consistency as possible internationally. We will be hearing some more about that, too. Let me just say, around that, too, before we have Dr. Mayers come up, that we very heavily participated in that international effort.

Do you have a follow-up question?

DR. GURIAN-SHERMAN: Yes. I guess that issue is around kind of harmonization conceptually,

but the other question, in terms of enforcement, I think is relevant, again, because it goes to how much emphasis you might be able to put in premarket scrutiny versus postmarket. If it is more difficult to address a potential problem once it is on the market, from a legal standpoint, it has indications, I think, for the scientific issues because you may want to put a higher emphasis on your premarket considerations knowing that you have less of a handle on the postmarket. So that is why I was getting at that.

MR. LAKE: I'm sorry. I forgot--

DR. GURIAN-SHERMAN: There were two questions.

MR. LAKE: I forgot to answer your second question so let me respond to that a little bit. It is certainly true that the burden, basically, if we find something in the marketplace, whether it is bioengineered things or anything else, that is out there that we believe is in violation of the law, the burden is on the Food and Drug Administration to go into court and make that case.

By the same token, though, if, again, under the regime as it stands right now, there is nothing that requires a company to come to us and

say boo, although we strongly encourage them to do so and, so far, they have always done so and, after a lot of discussion with our lawyers, they agreed we could propose to require in the future.

But we would have the same situation if somebody simply went to market without consulting with us, we would have the burden of demonstrating that what they were doing was inappropriate. By the same token, I think it is also true that, if we were to apply a standard that is not clearly recognized by the law and we were challenged, we would have the burden in court to explain to the court why it is, under the law as it stands, that we are requiring this standard.

I think the concerns you are raising are important concerns. Again, I would just come back to I think they are really outside the purview of this discussion and are actually probably a lot more complicated than I have indicated. But I think, for purposes of this discussion, we really like your best advice on the science and, particularly, with regard, in this meeting, to the issue of allergenicity. Presumably, we will have other issues in the future.

DR. BRANDT: Other questions?

DR. KAPUSCINSKI: Anne Kapuscinski. I would just like some clarification from Dr. Maryanski, or if you want to answer. It doesn't matter. I think it was towards the end of your presentation, you said something to the effect that you are looking to this committee to advise you on science issues that are in the guidance document for the current kinds of proteins you have been looking at?

I had maybe misinterpreted, in the briefing documents, that you actually looking forward more to the new things that you are know are coming, the dietary supplements, even the fact that some crops that might engineered might produce some kind of pharmaceutical or some kind of health product, they might desire to put parts of it into the food supply.

So I would appreciate clarification. Is it just that narrow group of metabolic enzymes you have seen up to now or do you want our input on this other stuff that is waiting in the wings?

DR. MARYANSKI: That is a good question. Let me try to clarify that. In terms of actually developing draft guidance for the proteins in bioengineered foods, it is our sense that the

guidance that you are going to hear about in terms of the international guidance has been developed mainly with an eye to the kinds of products that we have seen to date.

So, in terms of drafting our guidance, we are going to primarily be thinking about that. That is what we want to do first because we expect to see a number of products down the road that will be very similar. So that is the highest priority.

Now, we obviously realize that other products are going to be coming in the future, too. So we do have an eye to the future an we, obviously, are interested in your thoughts about that to the extent that you might have some. But I think, in terms of the priority and the focus for helping us get to the next step of producing a draft document that then you can look at again, we would like the emphasis on those substances that were seen at this time that we have seen in the past.

Is that helpful?

DR. BRANDT: Yes; but that doesn't keep you from looking to the future, is what he is trying to say.

DR. MARYANSKI: Right. That is what I am

trying to convey to you is that, if you have thoughts about things that you think we need to know about in the future or look at in the future, we welcome those thoughts as well.

DR. BRANDT: Other questions?

DR. BUCHANAN: Bob Buchanan. The current President of the Deutsche Forschung Gemeinshaft, the DFG, and I were post-docs together in Berkeley not that many years ago and we have kept in touch. He tells me that the German government often consults the FDA with respect to new pharmaceuticals that are emerging and to be marketed.

I see now that this cooperation at an international level regarding bioengineered foods but I wondered, is that a new thing or have governments, in the past, consulted the FDA for common problems?

DR. MARYANSKI: Yes. I think we don't consult with all governments on a routine basis but we do consult with other governments on specific issues. We do, for example, have dialogue with the European Union at the agency level on food issues generally.

DR. BRANDT: But the Codex was put into

effect thirty-four, thirty-five years ago. So that has been going on for a long time.

DR. MARYANSKI: Yes. Most of our work is done through the Codex in terms of our international work with other governments. That provides the mechanism for us to talk to other governments.

DR. BRANDT: I can tell you when I sat on the board of the World Health Organization, the Codex was regularly brought to us, the Codex discussions regularly come to us just for information and sometimes action we had to take to implement them or otherwise. So it has been around for a long time and intermittently effective.

DR. GURIAN-SHERMAN: I would like a little further clarification on what you want from us.

DR. BRANDT: We are really going to talk about that a lot tomorrow.

DR. GURIAN-SHERMAN: I can wait until then, if that is better.

DR. MARYANSKI: It is summarized in that paper that you have on charge and questions.

DR. BRANDT: The draft that you have in front of you.

DR. MARYANSKI: When you get a chance to

look at it, which we haven't given you just yet.

DR. BRANDT: You just got it today, so you can read it tonight and then we can talk about it. That is one of the reasons why we don't want to talk about.

Other questions? Hearing none, we are going to break. According to the official time clock, it is 2:45 p.m. and we reassemble at five after 3:00.

[Recess.]

DR. BRANDT: We have on the next agenda item where we are going to be talking about the draft Codex and the assessment on possible allergenicity. The document is Tab 9, in front of Tab 9, in your book. The actual section begins on Page 12 of that.

Dr. Mayers, we are ready for you.

Codex Draft Annex on the Assessment of Possible Allergenicity

DR. MAYERS: Thank you, Mr. Chairman.

[Slide.]

I am Paul Mayers. I work in the Food Directorate in Health Canada. My colleague, Jim Maryanski, commented that I was an expert in the Codex work. I don't know that I would take it that

far. I have been involved a lot with the Codex work and so when the kind invitation was made to come down and talk about it, I was more than happy to do that because, obviously, we are going to be very interested in Canada in the output of what you do here because we have done a lot of work together, all through this Codex process. Where you go from here in terms a national strategy is obviously going to be very interesting and relevant to us.

[Slide.]

Since you have already had the introduction of Codex in general, let me start with the Codex ad hoc Intergovernmental Task Force on Food Derived from Biotechnology because this is the body in Codex which has been charged with the development of guidance pieces around food biotechnology.

It was established in 1999 and with a specified time limit to develop standards, guidelines or recommendation for foods derived from biotechnology and was very ably hosted by the government of Japan. As I mentioned, being time limited, they are intended to complete their mandate by next year.

[Slide.]

As part of facilitating the process which, within that short time period, if you have had any involvement with Codex, one of the things that you will probably have taken note is that Codex tends to work in glacial time. Standard setting in that Codex process within the time-limited period of this task force was going to be a challenge.

In order to accommodate that challenge, FAO and WHO, committed to supporting the work of the task force. The mechanism that they used in terms of that support was a series of expert consultations.

At the very first session of the task force, the issue of allergenicity was already very much right at the center of the challenge faced by the task force. They put forward a question for consideration by a joint FAO/WHO consultation and that was what scientific approach can be used to assess allergenicity, a fairly broad question and a fairly challenging one.

Of course, the expectation was that the outcome of the consultations would contribute to the consideration in the work of the task force.

[Slide.]

FAO and WHO have certainly been active in this area with expert consultations both before the genesis of this task force and Codex as well as since that time. I have noted here three in particular because, in each of these three consultations in 1996 and 2000 and in 2001, allergenicity formed a part of the discussion.

Of course, in the 2001 consultation, it formed the very basis of the consultation and each of these pieces continued to contribute important considerations to the debate that was going on internationally around addressing this particular subject.

In 1996, and again considered in the 2000 consultation, there was a decision-tree approach that was available for consideration and had been considered by the expert consultation. Within the context of that decision-tree approach, not unlike what you heard in Dr. Maryanski's presentation, considerations related to the source of the introduced protein, impact of the actions on that protein such as digestion and processing, and sequence similarity to known allergens were key considerations.

[Slide.]

Here you see what that decision tree looks like and you will note that there are two sides to the tree determined by the outset by the nature of the source of that introduced material. So where it is not a known allergenic source, then the physical, chemical characteristics of the protein and its stability to digestion and processing being used to contribute to an identification of the potential for allergenicity and, down the other side, where the source is known to be allergenic, a more direct application of the available tools using solid-phase immunoassay as the mechanism.

There was a certain level of confidence with one side of this. The other side continued to generate questions. So, in 2001, the expert consultation which focused very specifically on allergenicity introduced new elements to the approach, elements that responded to the questions but also elements that were taking into account interests, challenges, new developments.

So a couple of issues to highlight from their report was that, in addition to the sequence-homology analysis from allergenic and nonallergenic sources being considered, that the issue of targeted serum screening would be added to the

specific serum screening as a strategy, the targeted serum screening being added with the intent to identify allergens that might not be caught with the other strategies.

The narrowed the physical characteristic focus to resistance to pepsin, quite specifically, and introduced, as an additional consideration, the use of animal models in the strategy.

[Slide.]

So, we now see, then, a revised decision-tree strategy having been proposed as the result of the 2001 expert consultation. You will note that, while there continues to be the question regarding the source of the gene and its known allergenicity that the two sites interact much more than they did previously through the consideration after sequence homology in both cases of targeted and specific serum screening dependent on where the first question led.

[Slide.]

This all, then, became fodder for the discussion in Codex. The output of these expert consultations were taken very much into account during the discussion in drafting general principles and a specific guideline document in

Codex. The work of the expert consultation on allergenicity specifically was considered very useful, but it was recognized that it also proposed a very significantly different approach.

In addition, in the discussion, many delegations expressed a real interest in what was presented by the FAO/WHO expert consultation but questions remained regarding the practicality of certain parts of the strategy proposed in terms of the ability to apply them currently with the level of development of tools such as, for example, animal models.

So, to allow for a more detailed consideration of the allergenicity assessment procedure than would be permitted in an open-forum Codex discussion with 65 country delegations and, in addition to that, another 40 or so nongovernment delegations, the task force made the decision to create and an hoc open-ended working group to develop guidance for consideration by the broader task force.

[Slide.]

So, in consideration of this ad hoc open-ended working group, it was requested to take into account the information that was available

including the output of the 2001 expert consultation. The government of Canada was asked to take the lead for the working group. Canada agreed to do that and convened the working group September 10 to 12, 2001 in Vancouver.

It was my privilege to chair that working group. You will probably have taken note in the dates of some of the challenges that that group faced, and I must pause and commend those members of the working group because I know that it was a tremendous challenge, one to continue the work in that period, which all delegations agreed to continue, and, two, many of my colleagues ended up with some tourist time in Vancouver that was unplanned, as you might imagine. I know some took some interesting routes to get back to their homes and, for some, it was a lot later than they planned.

So the government of Canada very much appreciated the commitment that delegations made to completing the working in such trying times.

[Slide.]

So, in terms of the work of the working group, we started the proceedings with consideration of a discussion paper that had been

prepared by a drafting group. We felt that it was very important to put before the group, in order to progress the work, a paper developed by a smaller group that would raise questions, propose strategies and take into account the range of information that was available at the time.

We also benefitted from the presence of the secretary of the FAO/WHO 2001 expert consultation who made a presentation on the work of that expert group because we thought that it was very important, as a starting point, to start from where that group concluded in terms of their recommendations.

In organizing the guidance, within the working group, the decision was taken to organize it rather than a single schematic into two parts, an initial assessment that would be the practical solution to consideration of the steps that would likely be taken anyway and then the subsequent detailed considerations based on the output of that initial assessment.

There was a very clear recognition that the initial assessment was not intended to be conclusive but that these were the considerations that would be relevant to all expressed proteins.

So you see, as I go forward, the group tried not to focus on guidance that might be construed as yes/no questions. There was a concerted decision to move from that style of guidance to a broader style which has its detractors, I can guarantee you, because, as always, if the questions aren't definitive as yes/no, it introduces a level of interpretation that can be challenging, and I think appropriately challenging, because of the nature of the issue being considered.

But I can also note that it does raise questions for some.

[Slide.]

So, as we worked forward, what we wanted to do was introduce, consistent with the rest of the guidelines--and if you have taken the time to look at the totality of the Code guidance, not just the part on allergenicity, you will take note very quickly that none of the guidance provides a simple yes/no answer.

In fact, throughout the guidance that the task force was already very advance in elaborating, there was a very strong influence of weight of evidence as the consideration being undertaken.

So, in the working group, that contribution, in terms of weight of evidence, influenced the way that the working group concluded and put forward recommendations back to the full task force.

In having reported back to the task force, in plenary, the task force was able to undertake a I wouldn't say detailed but an extensive discussion of the proposals of the working group and while certainly made modifications, many, I think significant improvements, the general strategy proposed by the working group was accepted.

[Slide.]

So, in terms of that strategy, by way of introduction, it focused specifically in IgE-mediated allergenicity. There had been an interest expressed to also consider celiac disease, for example. The working group didn't believe that it had the competence to address that particular challenge in the same way that it would the IgE-mediated and so limited its focus to IgE-mediated allergenicity.

The approach, therefore, rather than a decision tree was an integrated stepwise but still case-by-case approach. Case-by-case here doesn't mean that you reinvent the strategy for each

product. What it means is that the strategy needs to take into account the nature of the product and be appropriately tailored to address the issues raised by the nature of the product, itself.

Of course, in terms of the goal, the endpoint of the assessment is a conclusion as to the likelihood of the protein under consideration being a food allergen.

[Slide.]

The strategy, as I mentioned, starts with an initial assessment consideration. These are things that you certainly heard in the presentation earlier, the source, the amino-acid sequence homology. I must note here that the working group had significant discussion around the actual process of sequence-homology assessment because there had been significant interest in fixing a number of contiguous amino acids that would be used for the search.

The discussion went back and forth between six amino acids and eight. There was a recognition that, at eight amino acids, there were concerns regarding misses that would yield false negatives and, equally at six, there were concerns related to hits that would yield false positives.

In typical Codex fashion, after much discussion, the working group decided that, rather than fix a specific number, instead it would recognize that, for a valid search, consideration needed to be given about the appropriate number for the nature of the product under consideration and that the number selected should be based on an appropriate scientific rationale.

So, rather than fixing a number in the guidance, it recognized the issues in terms of both false negatives and positives but created flexibility in defending the selection that is made in order to carry out the test.

DR. LEHRER: Could I ask a question?

DR. MAYERS: Of course.

DR. LEHRER: Sam Lehrer. I have a question about appropriate scientific rationale. Could you be a little more specific about that?

DR. MAYERS: In terms of the rationale, the expectation would be, and this is where national governments as opposed to Codex will have to make decisions because Codex doesn't make decisions about products. It has provided guidance.

National governments have to interpret

that guidance. National government will have to apply that reasoning, so let me speak to it from the Canadian perspective, if you will allow. In this case, for us, an appropriate scientific rationale would be a detailed discussion on the selection based on the information available regarding amino-acid-sequence tests where six or eight or twelve, if someone selected to do that, were conducted in terms of rates of false positives and false negatives and the arguments that might be available if we are dealing with a particular category of allergens in terms of issues like epitopes.

It is not something that I am going to suggest is cut or dried. I believe that each argument is going to have to be carefully considered. I would hope that we will get to a point where we will have seen sufficient arguments to begin to characterize that particular guidance more specifically but I can tell you right now, we are certainly not ready to do that in Canada in terms of fixing a number.

So what we are doing for each product, what we are looking for is not just the results of the homology comparison, but we want some

discussion around the validity of that comparison in terms of addressing the issues of false negatives and positives.

I know that is not as specific as I would like it I were asking the question but, unfortunately, that is the reality.

DR. BRANDT: Go ahead and finish up your presentation. We will come to questions

DR. MAYERS: Continuing, then, with that initial assessment portion, the structural properties including issues like susceptibility to enzymatic degradation, heat stability and acid processing.

[Slide.]

Once we get beyond that initial assessment consideration, then we get into the more specific considerations. For proteins originating from a source known to be allergenic or with sequence homology, then specific serum screening recognized as being a very useful tool.

Where those proteins are not coming from an allergenicity source or not exhibiting the homology, then consideration of target serum screening--and you will note the "may" here; that "may" was very important given concerns expressed

regarding the validation of targeted serum screening strategies.

There was a very clear recognition of the utility of the tool recommended by the 2001 expert consultation, but there was an equal recognition that work needed to take place in order to facilitate the use of this tool by developing more clear strategies and validating them.

Recognition in terms of this part of the consideration, that the results from in vitro amino assays may not, in fact, be sufficient. So a negative result where this was warranted, again taking into account the totality of the evidence as opposed to simply one aspect of that evidence may, therefore, prompt additional testing, a positive result being considered an indication of a potential allergen.

[Slide.]

There were, of course, other considerations that were highlighted in the draft annex; the nature of the product, itself--i.e., the form to be consumed being taken into consideration in determining for the strategy what types of processing would actually be taken into account, so, rather than automatically defaulting to a

particular set of processing tests for the protein, taking into account the food product, itself.

So, again, when we say case-by-case, we are not talking about making it up as you go. Instead, what we are talking about is structuring the strategy to most effectively deal with the particular product under consideration and the recognition that both the targeted serum screening and the use of animal models have tremendous potential to add value to the assessment but require validation in order to allow regulatory agencies the level of comfort in their application that would be appropriate for regulatory decisions.

[Slide.]

Also, recognizing that while calling for serum screening is very useful, the availability of sera represents a very real challenge. So the need, in order to facilitate that work, the organization of an international serum bank, for example. Further, even more detailed assessment may be possible once methods related, for example, to examination for T-cell epitopes and structural motifs, which are associated with allergens, are appropriately evolved to applied in regulatory decision making.

[Slide.]

The task force, having taken into account the report of the working group and, having had its discussion, made some decisions and I have indicated here some of the next steps. It referred the issue of the gluten insensitivities to the Codex Committee on Nutrition and Foods for Special Dietary Uses for their information.

It wasn't possible for the task force to go beyond information. That Codex committee will have to make decisions as to whether they are at a stage where they could consider more detailed work in terms of gluten insensitivities, for example.

The Annex was advanced to Step 5. In the Codex process--I know we didn't give you Codex 101, but, within Codex, for a standard to be adopted, there is an eight-step process. The Annex was advanced to Step 5 of that Codex procedure and forwarded to the commission with the recommendation that it be adopted at Step 8, which is the final step, with the omission of Steps 6 and 7.

So that means, once considered by the commission, in June of next year, then if accepted by the commission, including acceptance of the recommendation to omit Steps 6 and 7, that Annex

will then be adopted as part of a Codex standard.

The full Codex guideline and the principles have been forwarded, as well, to the commission for consideration at Step 8 of the procedure.

[Slide.]

Finally, since, having come from Canada, I believe I would be remiss if I didn't give you at least some insight into some of our thinking in regard to some of these pieces because, we, too, have been thinking very hard around the issue of allergenicity and continuing to enhance the addressing of allergenicity in our guidance.

We have undertaken a couple of initiatives that I would note. One, in November of last year, we held an international workshop on animal models for the detection of allergenicity and, from that work, we have continued to integrate into the research program in the Food Directorate in Food Canada where I work some research initiatives regarding the issue of models.

We are, as well, pursuing some research partnerships with regard to new tools for the assessment of longer-term health effects including toxicology where, in particular, we are focusing on

the issue of whole foods and biological markers of relevance in toxicological assessment so as to enhance the toxicological testing element of our assessment strategy.

You may have taken note that the Royal Society of Canada, at the request of our department, along with others, had formed an expert panel which provided us with recommendations so we are now in the process of updating our guidelines for the safety of assessment of novel foods. We expect to have a draft in consultation in the fall which will take account of those recommendations as well as the guidance by Codex.

We are a bit ahead of the game in that Codex has not formally adopted them but we have been appropriately impressed with the work accomplished in Codex and so we believe that, even without their adoption, there are interesting elements presented in the Codex guidance that we would like to see brought into our strategy earlier rather than later.

We are also doing some work on guidance for transgenic animals which, hopefully, we will have open consultation later this year, but that is not particularly relevant to this discussion so I

won't take that any further.

So, Mr. Chairman, I will be more than happy to try to take questions.

DR. BRANDT: Thank you.

Let me remind all of you that tomorrow, on Question No. 1, that they are seeking advice has to do with the Codex because, specifically, every national government now has to address it totally independently, as it were, because it is not imposing rule.

So Question No. 1 that we will be talking about tomorrow, as listed in your two-page document, will be addressing that specific thing.

So let's go to questions.

Questions of Clarification

DR. GURIAN-SHERMAN: Doug Gurian-Sherman. Two questions. One is, could you clarify a little bit what the steps that the current process is at and are there provisions in Codex to modify a final decision. Do I understand correctly, the task force has recommended to Codex to accept the Annex; is that right? And then what is the procedure for the full Code committee? Can they modify it? Can they just accept or reject? That is the first question.

The second question is, going back to the 5 and 6 contiguous amino acids, did the FAO--did the task force decide--I want to be clear about this--that, if you set eight amino acids as the limit, that you could miss active epitopes. So then the question becomes how do you justify the false positives? Either the greater false positives for six or the greater false negatives for eight? Is that an accurate assessment of what FAO decided?

DR. MAYERS: Let me take the first one and then, if I don't remember well enough, remind me. In terms of the procedure, the commission will have the flexibility to adopt based on the recommendations or to not adopt. That is why they are the commission.

They also will have the flexibility to make decisions in between, if you would, in that they might ask for further consideration of specific issues. That will be challenging, given that the commission will be meeting after the mandate of the task force itself is complete. That means that there won't be a body to refer that work to, but that doesn't mean that the commission has to adopt the guidance whether it be principles, the

guidelines, or, specifically, the Annex.

In terms of the step procedures in Codex, the procedures are there to ensure that there is appropriate input from delegations. So, along that path, certain steps of the procedure involve consultative mechanisms. One consultation mechanism has been engaged and the proposal to eliminate two steps would remove one of those consultative mechanisms. It hasn't removed all of them, but it would remove one.

In terms of the other issue, in terms of the working-group discussion around the contiguous amino acids, there was sufficient recognition that, within the working group, we didn't have enough information around the impacts to fix a specific number, nor did we have sufficient time to analyze the issue sufficiently deeply to propose a specific number, that the issues of false positives and false negatives were both relevant.

So there wasn't a simple balancing of, well, we might hit it or we might not. It was simply a recognition that fixing a specific number with the current knowledge would be inappropriate at this time and so, therefore, the proposal that, instead, the approach taken for an individual

comparison would need to be defended, based on the nature of the comparison, itself, and the product under consideration.

DR. BRANDT: Other questions?

DR. KAPUSCINSKI: Anne Kapuscinski. You seem to indicate that there is a clear distinction between the weight-of-evidence strategy and the decision-tree strategy. When I reviewed the documents we have about this Codex endeavor, it seemed to me like the two go hand-in-hand. It looks like the decision tree is just a way of kind of visually showing the order in which you deal with the different lines of evidence so that then you do actually consider the whole weight of evidence.

So am I missing something?

DR. MAYERS: I don't think so. I would share your interpretation. The only challenge with the decision tree wasn't the questions that are posed. It was the fact that it identified yes/no answers. Some of the answer are going to be made--

DR. KAPUSCINSKI: Are not flexible; right.

DR. MAYERS: So that is really the issue.

DR. KAPUSCINSKI: I have one more question. In at least one of the Codex documents,

I think it was the joint FAO/WHO expert consultation, there is a lot of talk in there about suggesting further study for postmarket surveillance and monitoring.

Since it seems to be couched mostly in the general language of suggestions and rating some issues to be considered, what do you think will happen after the CAC meets in 2003 regarding that particular issue?

DR. MAYERS: The issue of postmarket surveillance is dealt with quite specifically in the principles document, in the FAO/WHO expert consultation, being an expert consultation, it provides recommendation while the Codex has the responsibility for the standard setting.

So the language in the Codex principles is more specific. It recognizes that postmarket surveillance may be a very valid tool where a specific question is identified and the strategy for postmarket surveillance is designed to respond to that question.

What it doesn't do is it doesn't simply propose that postmarket surveillance always be applied for every product.

DR. GURIAN-SHERMAN: I have one more

question. This is Doug Gurian-Sherman. Back to Anne's question of the decision tree versus weight of evidence. I have heard some definitions of the decision tree that suggest that, of course, I think there is pretty wide recognition that, let's say, with the digestibility assay, if you get stability, it doesn't mean that something is going to be an allergen or vice versa.

So that is a maybe answer. But I think, in terms of decision making, some definitions of the decision tree suggest that, if you got a certain answer, that we be a no-go on the product whereas, in weight of evidence, you are considering everything and putting them altogether and saying, well, we got this answer for this and this answer for this. Based on our understanding of all of these together, we make this decision. Is that correct, because that is certainly a difference that I have heard debated and that there is a certain amount of concern about, I think, in the consumer community.

DR. MAYERS: I think there are a range of interpretations. That is part of the challenge with trying to simplify a complex assessment strategy in a pictogram. But, a pictogram is very

powerful because it gives you insight. Personally, I am a bit torn. I like the simplicity of understanding the totality of what you are trying to do that a pictogram represents.

I do get concerned if the interpretation then becomes so rigid that we forget that we are dealing in a scientific endeavor with questions that don't always lend themselves to a simple cause-effect response especially if we are dealing with something like the results of a digestibility assay.

DR. BUCHANAN: This is Bob Buchanan again. Assuming an ample international serum bank, is there some way that targeted serum screening can give information as to whether or not a protein to which human populations have not been exposed in their diet, dietarily, can be assessed to be an allergen?

DR. MAYERS: That is a great question. I think there are people in the room who are probably way better than I to answer that because that, in itself, is, I think, a very interesting and significant debate. But I certainly hold some hope that targeted serum screening will give some insight. I don't know if it will answer that

question but I think it certainly can contribute effectively if there is a good bank of sera against which to challenge a particular protein.

But I certainly don't have the expertise to take that particular debate to its fulfillment, I don't believe.

DR. ATKINS: Dan Atkins. You mentioned that the stepwise approach was a bit more cumbersome. We talked about six versus eight amino acids. But we are not challenging people anywhere here. Part of the thing that concerns me about that is that, if you take, for example, fruits and vegetables, if your RAST assay or ELISA doesn't incorporate all the allergens, or they are different in fresh products, now you are going to have a negative test, you are going to open this up to everybody, and there is a population that is going to react to that and you are going to miss them in your whole process.

So, are food challenges going to be incorporated in here at some point before we release this into the general population or not?

DR. MAYERS: When you say "food challenges," I had to respond with a question, but who are we going to challenge?

DR. ATKINS: You have a population that you are going to say they are important enough you are going to look at their serum to see if they are allergic to the product, so why wouldn't you challenge them, for example?

DR. BRANDT: Remember that that is a point you can really raise with the FDA because each country is going to have to make that decision. It is not going to be an issue that that task force or the Codex or the WHO or the FAO is going to decide.

DR. ATKINS: What they did was they dropped out the challenges of individuals in the first study and then they went away from the step-wise approach to the weight-of-evidence approach which means you can say, well, we, as a group, want to discount this data because we don't think it is that important. Would you get the same if you had several groups? Would you get different opinions? How do you defend that to the public. How do you explain that to the public? It is okay this time? It is not okay that time? It is going to make it harder.

DR. BRANDT: It is advice, though, that we can give the FDA about further steps.

One more question and then we are going to

quit.

DR. ASTWOOD: Jim Astwood here. I was going to follow up on Dan's question. Just for clarification, in the original '96 and in Year 2000 FAO/WHO expert recommendations, the food challenge appeared and was recommended in cases where the source of the gene was from something known to cause allergies.

So the debate is around whether that should be in or out. As a practical matter, I am not aware of any product, and Dr. Maryanski could confirm, that the FDA has considered where such a gene has actually be put into a crop and a petition has been made on it. So there is a certainly element of hypothetical consideration there, but it is an important point.

DR. BRANDT: Okay. We are going to meet again at 8:30 tomorrow.

[Whereupon, at 3:50 p.m., the proceedings were recessed, to resume on Wednesday, August 14, 2002 at 8:30 a.m.]