



SOT FDA Colloquia on Emerging Toxicological Science: Challenges in Food and Ingredient Safety

**October 11, 2018—The Big 8: Advances in Food Allergy
Risk Assessment and Management**

US FDA, Wiley Auditorium, College Park, Maryland • Live Webcast

Real-Time Captioning

Note: This is not a transcript.

October 11, 2018

The Big 8: Advances in Food Allergy Risk Assessment and Management

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US FDA Welcome and Overview

Susan T. Mayne, CFSAN Director, US FDA, College Park, MD

Good morning. It's my great pleasure to welcome you all here today to the center to join us in today's SOT FDA colloquium. Today's event is part of a very successful partnership between SOT and [inaudible] to bring leading toxicologists to the table to discuss future oriented sites relevant to the safety of food and food ingredients.

As noted here, our purpose today is really to focus on sharing science. This is important to us at FDA because we are a science-based regulatory public health agency. Strong science is the foundation of everything that we do. I am always impressed by the quality of the science that is presented at these SOT FDA colloquia. Today we will discuss scientific issues involving major food allergens. Allergens in foods are of great importance to us here at CFSAN. Food allergy is also of great interest more broadly as reflected in the attendance we have here today. We have 335 people registered for this event with 275 webcast registrants and 60 people registered to attend in person. Our webcast attendees include 49 participants from 17 countries outside the United States. Just this past week, there was a story in the Washington Post Magazine entitled "It's Bad Enough to Have a Food Allergy but Then You Have to Deal with the Skepticism." The story highlights the fears consumers face in avoiding many types of potentially hidden risks posed by food allergen. The story also shows that there is public misunderstanding of what are the two allergens and allergenic risks. This is an area where the colloquia such as today with clinicians, researchers, the food industry have an important role in educating the public about allergens and the importance of understanding risks and managing true allergen hazards.

In giving this morning's introductory remarks, I think it's important to provide a very brief overview of how we got here and what we are doing at CFSAN to help consumers avoid harmful allergens. First, how do we get here? FDA's first efforts to address the problem of undeclared food allergen was issued a notice to ventures a labeled [inaudible] in 1996. Think about that. It's two decades ago. It recommended that manufacturers label ingredients. In 2001, FDA issued an allergen compliance policy guide to further adjust labeling and preventing cross contact of common food allergens. To make it easier for food allergic consumers and their caregivers to identify and avoid foods that contain major food allergens, Congress passed in 2004 the Food Allergen Labeling and Consumer Protection Act. It identified eight foods or food groups as the major food allergens. They are milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. It also requires manufacturers to label food products that contain any ingredient that is or contains proteins from one of the eight major food groups I just mentioned. It also required FDA to define the term gluten-free and permit the voluntary use of the term on food labels. The final rule finding gluten-free was published in 2013. Allergens have also been formally addressed in the risk-based preventive controls mandated by the Food Safety Modernization Act of FSMA. Food manufacturers are required to implement a food safety plan that includes safeguards to prevent or significantly reduce hazards such as undeclared food allergens by cross contact.

What are we doing about allergens beyond labeling? They are the leading cause of food recalls requested by FDA. CFSAN is working on many fronts, three in particular, to reduce the number of such recalls. First, research and the cause of these errors, consumers can help by reporting food allergic reactions to the Adverse Event Reporting System, and to FDA's consumer complaint coordinator in her district. We are trying to learn what foods are most commonly associated with food allergic reactions, what allergens are most involved, and how labeling errors might have happened.

Secondly, working with industry on best practices, for example, recall data shows that labeling errors commonly occur because of the use of the wrong label. This may happen when similar products made with different ingredients including allergens are sold in look-alike packages. Recall data give us the opportunity to reduce food allergen recalls through improved industry awareness and simple changes in the way that packages, labels, ingredients are handled and tracked within production facilities.

Thirdly, developing new ways to test for the presence of allergens, in this arena, CFSAN research has been developing [inaudible] which is the profiling approach for detecting allergens. That can simultaneously test for 14 different allergens including gluten.

We will discuss prevention of food allergies. I will mention that last year, FDA allowed a qualified health claim advising that early introduction of peanuts to certain high-risk infants may reduce the risk of developing a peanut allergy. This qualified health claim reflects paradigm changes in science including a major trial published in 2015 that demonstrated that introducing peanut containing foods to infants at high risk for developing peanut allergy was safe and led to an 81% reduction in the subsequent development of peanut allergy. This is an example of important science surrounding food allergy that is continuing to evolve. Let me conclude my remarks so we can move on to hear about exciting science that has potential for real public health benefits. On that note, my next step is to introduce Brian Delaney, chair of the SOT FDA colloquium series. You can come up and take a microphone.

Welcome from SOT and Introductions

Bryan Delaney, SOT FDA Colloquium Committee Chair, Corteva Agriscience™ Agriculture Division of DowDuPont, Johnston, IA

Thank you for coming this morning. I see familiar faces out there. I will be quick in my introduction for the speakers. Today is a full schedule of true experts in food allergy. I am thankful for their participation and for the people in the room and on the phone. I want to start briefly about part of the Society of Toxicology mission overall and for this series specifically. It is to create a healthier safer world by advancing the science and increasing the impact of toxicology. We want to strengthen the relevance and impact of toxicology, support toxicologists, and expand outreach and impact globally. I think you for the introduction and welcome everybody on behalf of SOT. A brief history of the series is that this is an FDA sponsored event and SOT is the organizer. Folks are primarily on food ingredient safety, it started out in 2014. We started as a one-year proposal and we have done the 16 of these so far. We have 70 people registered on-site and around 300 online and it's also available for your friends and colleagues who have an interest who were not able to attend. You can see here there are the number of downloads for the different presentations we have had over the years. You can see that the total at the bottom is 86,934. I do not know how many toxicologists there are in the world, but I know it's not that many. This is an interest well outside of the field of toxicology and it's a limited set of data from which the downloads have been reviewed. You can see the genetically engineered plants has been downloaded 29 times and we just did it a couple of months ago. If you come back in a year or year and a half from now, it would be a larger number of those being downloaded.

Thank you to the organizing committee for the colloquium. [inaudible] quantitative risk assessment [inaudible] assessment of the allergen via food produced two egg biotechnology. He is heavily involved in outreach in the food industry and allergies and sensitivities and has

helped countless companies on a wide range of topics. I worked with him for 25 years in one level or another. [inaudible] he is a medical officer and allergy specialist currently [inaudible] applied nutrition at the U.S. FDA. Is also a clinical teaching faculty at Georgetown in Washington DC. His responsibility includes assisting in coordinating FDA activities and policies, to manage food allergens in [inaudible] his research interests are aimed at understanding [inaudible] assessing the health impact of allergen thresholds. He completed medical school and residency training at Georgetown University medical school and fellowship in allergy and immunology at the national Institute of [inaudible] with that, I will turn this over to Dr. Taylor.

Taylor: Thank you. It's good to be here and I'm pleased to help organize this event. I think we have a number of excellent speakers. Without further ado, I will introduce again my cochair, Dr. Stefano Luccioli will give the first presentation on the public health burden of food allergies and what are the challenges.

The Public Health Impacts of Food Allergies

Stefano Luccioli, US FDA, CFSAN, College Park, MD

Thank you. I get to have the important assignment of trying to frame what we are going to be talking about today. This is the title I have chosen. It would probably be better if we talked more about the verdant of food allergen avoidance because that is an important of what we do in the center. But I just wanted to also say I have no conflicts. But I do have a disclaimer for at least one slide. I think for the spirit of this type of series, we want to talk about scientific issues. There are some important scientific issues where we are still evolving in policy. So, I do not want to say that this is policy. So, my focus of today is to define food allergies. I think we have to understand what are the underlying issues with people who are living with food allergies, what are the nuances in terms of diagnosis, what we know about prevalence and risk prediction and so forth. We will talk about regulatory activities and also talk importantly about what are some of the risk assessments with regard to helping consumers avoid allergens with focus on thresholds.

I want to start with the clinical case. This is a 46-year-old male, long-standing springtime allergy, asthma, penicillin allergy with eating a leftover tuna steak from last night's dinner. There was a headache, diarrhea, shortness of breath, high blood pressure. Is this a food allergy? Is kind of interesting. It's tuna which is a fish allergen. You can certainly develop an allergy even as an adult. Another thing that stands out is high blood pressure. Typically, allergic reactions are associated with low blood pressure, but this is more of a toxic reaction. This is actually Scombroid food poisoning. I thought it was appropriate for a toxicology meeting to talk about this. But basically, this highlights the many different types of adverse reactions that we see and are reported to our center. We have to sort through ones that are more important with regard to food allergy versus others. But the toxin Scombroid example is more of an intolerance. It's really due to adjusting a toxin.

When we are talking about food allergies, we talk about immune mediated reactions where the body makes a response to the food and as you can see here, there are many different types of immune mediated food allergies including celiac disease. We talk methodology, we are really talking about this group on the left, the IgE mediated food allergy which is important because reactions can be quite immediate and life-threatening and even fatal. So food allergy, as I mentioned, there is an adverse reaction to food that is IgE antibody mediated, involves a lot of proteins, a lot of foods, most of them commonly consumed in the diet including peanut, soy, egg, milk, wheat, treenuts, fish, shellfish. Over 170 foods have been recognized to cause IgE

mediated responses. Some include sesame, mustard, celery, lupin which are recognized in other countries but also we need to be mindful of these as the food supply changes and these may become more important. The prevalence, there's not a lot of great prevalence data in the United States via food allergies, pretty much, I think, from what is available, we can say about 2% to 4% of the population has some form of a food allergy and it affects mostly children. It's both genetic and environmental. And although some food allergies are out, it's a left wrist for many. I put here that there is no effective treatment. Things are changing. We will hear a little bit about treatments as well. But for the most part, since you cannot really prevent allergic reaction, the only way to keep consumer safe from the consequences a food allergy is to label. Avoid the product.

In terms of mechanism, it is important to realize what is happening with food allergy. There are two distinct processes. One is a sensitization process. For some reason, individuals predisposed start making antibodies to fee proteins that they should not be making. Over time, these antibodies rest on the surface of cells. Over time, when that food, when it comes, and enough of it is present to cross-link these receptors, [inaudible] these are like little bombs. They are full of mediators and release a bunch of things. It's a reactivity. What is distinct about these is there's two different processes where we can focus on prevention or maybe even treatment. But they are different. With regard to sensitization, seems to be something taking down oral tolerance. Most people are not allergic to these allergens. They can eat as much of the allergen as they want they become tolerant. We don't really know what the causes are. We don't know if there is some dose affect, exposure, timing. With the peanuts, with young kids, there seems to be something in terms of feeding it in high risk children. But we still have a lot of questions. With regard to elicitation, these are people who already have an allergy. Their main goal is to prevent reactions. Even one dose, this is one dose that can lead to immediate effect. This is where thresholds are important. As you saw, this is a very explosive reaction and it will have an amplification mechanism. Symptoms can vary from one reaction to the next and from one exposure to the next.

This highlights tolerance and desensitization and the paradoxes we mentioned. Avoid the allergen to prevent reactions. When we talk about prevention and treatment, we actually favor giving the allergen or some kind of exposure because we are trying to push that person toward oral tolerance. There are some other treatments that are happening that are really done to try to prevent your body from reacting to exposure. It raises your threshold with regard to desensitization. The idea is you are giving low doses of the allergen that saturate your receptors is that when you encounter the allergen, they are not going to cross-link and react. However, once that effect stops, these receptors lose their antibodies. Now you are still susceptible again. Many studies have shown an effect of desensitization. In terms of getting to this issue of sustained, unresponsiveness, it has been a challenge. This is what an allergic reaction looks like these are some of the important symptoms that distinguish allergic reactions from other types of adverse food reactions. You get hives, swelling, conjunctivitis. It can be very traumatic for some individuals when they have these types of reactions. You can certainly and for their risk management decisions for future exposures. As I said, there are no treatments to prevent these reactions from occurring. Once they occur, people are instructed to use medications to reverse the effects.

With regard to symptoms, it is important to realize that skin, these are all cells that are in the surface. The types of things we see our skin, G.I., respiratory, and the worst case is the vascular system. You can get very mild or subjective symptoms what you see in the blue like itchiness or sketchiness in the throat versus more objective symptoms in the green. That's like the throat closing or hypotension is a serious reaction. It's important to realize that this is an

amplification mechanism. Severity points are variable. When somebody reacts to a food, they may just have, in many cases, very subjective reactions and that is it. It's short-lived and that's the end of their risk. In some cases, they can have that reaction and it can go right to anaphylaxis and potential shock. It's a challenge. We all agree that anaphylaxis and shock are things we want to avoid. But what about reactions that are just going to leave subjective or objective signs? They may be acceptable risks.

This shows what we know about some of the different major food allergens. It is important to note that the prevalence is higher in children than in adults. There are differences among different food allergens. Milk and egg are more prevalent as children. Those tend to be more grown. Why these foods and not peanut or tree nuts being outgrown, we do not know. That highlights another difficulty. This is not one type of problem. There are different types of food allergens maybe with different risks. I also want to highlight from this slide that, when you look at these types of studies, you have to look at the criteria that is used for these studies. Many studies based on self-reported data have prevalence of 13% of the population and those based on what clinical signs of food allergy are much lower. Probably 1 and 4 people walking around with a food allergy actually have a clinically diagnosed food allergy. Why is that? It's important to look at diagnosis. Diagnosis, to be a food allergic individual, you have to have both observed characteristics of the allergic reaction and also positive food skin test or IgE antibody to it. How many times, I mean, I am sure Matt has seen people, who have had a reaction to shellfish 20 years ago and they stop eating shellfish and then they come and get tested and they are negative for shellfish. So they are basing it on symptoms, maybe not getting it evaluated fully. And the same goes with the opposite and you go in with maybe some nonspecific symptoms that you tested and you may be IgE antibody to a lot of foods and you have this list of allergens saying you are allergic and stay away. So there is a challenge and I think we do need better diagnostic or we need to encourage better diagnosis for food allergy.

The gold standard for diagnosis is the double-blind placebo-controlled challenge. This is a very intensive study. It's really not done in a lot of community centers. But it is important to note. I want to go through the food challenge because I think this is important and will set the stage for some other talks. This is a unique type of dose-response model. People start, and unfortunately, depending on the type of reason you are doing the challenge, many times challenges are done to make a diagnosis. So the starting dose may not be as important. So that can also impact what does the levels we look at. But basically, you start with a dose and then you have an incremental, you go over a certain time, you wait, give them the next dose, you wait, no reaction, and until they have a reaction or they are able to tolerate the challenge all the way to the final dose, usually this is done over a few hours. Okay? So there are important differences in these challenge studies. There is different timing intervals, different doses, starting doses, and adverse effect, when you see the adverse effect, you can measure it either as the dose during the challenge where the person reacted which is 4x, or you can do that cumulative which is the 7x because you count everything there. Another important issue is the adverse effect which is usually done, not a typical dose-response or dose severity curve. An important point about the challenge is to prevent harm. You don't want to keep challenging people until they go to anaphylaxis. They start, they stop at the first objective sign. Usually it's an objective symptom. Sometimes people with repetitive throat or abdominal pain, they may stop the challenge. There are different types of symptoms that may cause the challenge to stop as well.

When you start looking at populations, we have the food challenge data now on different food allergens in a population, you start seeing curves like this. If you look at the, so, looking at this dose distribution curve, let's call it, the people all the way up on the right, the upper right corner, you know, those people are reacting a millionfold higher than the people down to gram amounts

the food allergen versus milligram amounts down in the left-hand corner. Now so is there a different population here that we can maybe give different risk recommendations to? It's a challenge because there's also data showing that, in the same person, a challenge to the same dose, they may have, or during the food challenge, they may have a difference in the threshold, maybe to a hundredfold difference. So that creates a little bit of uncertainty in terms of saying that your threshold is always here. Now are people appearing the right-hand ever that sensitive to get down to the left? Maybe not. So we still do not have very good diagnostic tools to help us determine that. IgE levels are useful. The higher the levels, it does predict the likelihood every activity to the dose, to the allergen. But they had very little correlation with severity. And although some studies have suggested that the higher dose also correlates with lower doses in the challenge, that has not always been substantiated. We need better biomarkers. There is promising data on component analysis whereby that is we are looking now not just at the food, but people are sensitized to specific proteins in the food. And depending on which proteins you are sensitized to, it may determine your risk for maybe severe reaction or so forth. It is a promising science. But we are still sorting out what this means. And again, food challenges would be the best tool. But they are not really done very often in practice, especially to help people understand what their personal response is. So we get to a point where the medical community and even the consumer community does not really know what their threshold is. And then if you combine that with the fact that we do not have any good treatments to prevent reactions, a lot of patients get the same kind of advice. And that is to avoid allergens to the most extreme measure possible and here is your EpiPen and good luck. It is unfortunate. I think also, I mean, I have to say, the EpiPen, although it's a life-saving measure, does absolve physicians from having this risk discussion. You have a reaction, you have something here to prevent it. So those people who are up there on the right-hand curve who are reacting to really high doses are still getting the same advice that people all the way down at the other end are getting.

So the public health burden, let's summarize that some of the important issues are here with the food allergen issue in the community, it led to psychosocial impact and decrease quality of life. Even though people with food allergy are normal, they look like us, everything, their quality of life is similar to somebody with diabetes or some other chronic illness. Because of their limited food choices, their fear of accidental reactions, every time looking at labels, these all impact quality of life. And that is something that we kind of forget sometimes that these patients are going through. Reactions, unfortunately, also determined this quality-of-life. Reactions are still relatively common, unfortunately, to food allergens. We have laws that prevent, labeling is over, a lot of these reactions are occurring, unfortunately, to products that are not required to be labeled as well so that is the challenge. If you look at symptoms like in populations of surveys, 30% to 50% of individuals will report one allergic reaction within the year of the survey. It's the number one cause of ER visits to the emergency room.

And one issue I want to talk a little bit more about is death. Even public-health documents do not really focus on this. And we do tend to report without. Some recent analysis has shown that it is probably not that high. The prior studies were based on extrapolated data from a few counties in the United States. But when you look at actual, better death report data, it is probably closer to 20 to 30 deaths per year. When you look at the number of risks, this is like somebody getting struck by lightning. Really it's maybe not as common a problem as maybe is expressed in the community.

Another factor that is important and also why prevention is important is that food allergies tend to occur early in life, during the part of the allergic March when you have a lot of eczema and you start making allergic responses. And what happens is that these individuals may develop

things such as allergic rhinitis or asthma. And having asthma and food allergies does increase your risk for more fatal reactions.

Some of the regulatory activities involving allergen, we went over many of these, so I will just go briefly through some of the activities in our center, implementing food allergen labeling laws and policy, guidance, and also enforcing the laws, inspections, analytical methods, we do health hazard and risk assessments, and also have a post-market surveillance program, CAERS. There's also other regulatory activity in other centers. You will hear about treatment studies. Those regulated under our other agencies in FDA Biologics. There are also other laws applied but there are other products regulated by other public agencies.

I will not go through this. But this is the Food Allergen Labeling and Consumer Protection Act. It's important to recognize that FALCPA is only apply to packaged food and dietary supplements. Does not apply to drugs, cosmetics, or other FDA regulator products. Importantly also it does not apply to foods in most retail or food service establishments. Many of you may have heard this week of the unfortunate cases of two deaths to a sandwich from a retail company. And this is unfortunately an area where we need more discussion where there is not a lot of regulatory oversight. Another important area that is not covered by FALCPA is the area of unintentional incorporation of undeclared allergen food by cross contact. Manufacturers may voluntarily place an advisory statement or precautionary allergen labeling, may contain, et cetera, to alert consumers to risk. When these estimates are used, they have to be truthful and not misleading and not used in lieu of good benefactor in practice. And Food Safety Modernization Act defines cross contact and allergens. You have to control allergens as you would any microbial or other chemical hazard. And so this is very important. This is where we hope a lot of mistakes and labeling errors will be corrected in the future. Guidance is still pending on this issue.

What are the challenges with regard, so we have got labeling laws, people recognize allergens and stay away, great, everything is fine, right? Well, no. Not really. Avoidance is difficult. There's limited food choices, first of all. A lot of products have allergens in them. And then there's also products with advisory statements. One U.S. survey found 70% of all products in a grocery chain had an advisory statements. And some product categories had 40% or more advisory statement. This creates challenges in terms of, and then the food allergen information does not really tell you what the risk is. It could say contains milk and have like eight drops of milk in a secondary ingredient at very low levels or it could be a massive amount of the protein. You do not really have that information. Of course, you can look at the ingredient list to see where it falls. But some products just use a contained statement and you do not have an understanding. Plus advisory statements, there are different types of advisory statements and people are looking to these advisory statement as many different risks which is not really the case.

And again, avoidance and advice, avoidance advice varies as well as peoples risk perception and acceptance. Unfortunately, we are seeing a trend of more risk-taking. A lot of surveys are showing that maybe up to 40% of consumers, even though national guidelines state that you should avoid allergen advisory statements, people are still looking for more food choices and consuming these products. And they are taking risks. And unfortunately, I will show you some data on a recent study, up to 31% of people now have accidental reactions because the disregard these labels. And combine all of that with the fact that, at the level of the industry, these hazards are difficult to control. Undeclared allergens have increased in numbers over the past 5 to 6 years and are now one of the most common causes of food related recalls. Labeling error is an important part of the reason and can be preventable. Not just that, there are products also, different types of products that have a different risk profile. There was a survey of U.S.

products, dark chocolate products, and found that 70% of these products that had an advisory label had detectable milk. And a lot of these had detectable milk levels at levels that would have caused a lot of people to have a reaction. So there are products out there that have advisory statements that are almost always going to have the allergen versus some that rarely have it. So there's a lot of differences in that. The National Academy of Sciences on food allergy expert panel recognized and does recommend risk-based labeling approach for this.

I wanted to talk a little bit about this study from the Netherlands. They looked at 157 people who they followed over a year. And 76 of those, 46% of those individuals reported a reaction to a food product. For 51 of those products, they did this analysis here, and you can see that, of those 51, only 19 were able to find the allergen that the person was allergic to. But of those, in those two categories, there was an equal amount with a precautionary label and without. There was a lot of variability in terms of what products are causing reactions to certain individuals. And then in this table also, I want to show you that cow's milk is consistently the number one cause of allergen recalls that we see for allergens here in the United States [inaudible] low levels. But some had levels in the 4000 5000 ppm. There something going on here. We also need to look at preventive controls to try to prevent these issues.

I want to spend the last part of my talk talking about other revelatory risk assessment activities and management. There's a focus on the thresholds. I will not have a lot of time to talk about novel foods and proteins I know a lot of people here are working in this area. But it's safe to say that we have been using the guidelines to try to prevent the introduction of at least known allergenic proteins into the environment. I think we have been fairly successful. However, high-protein foods, this is a new area that may be a challenge where maybe these foods at normal exposures are not going to cause a problem but what about when you them at really high-protein amounts and obviously it's a concern of cross-reactivity. This slide or graph shows you some of the important food cross-reactive food allergies. It's just to help you understand this. So if you have something like a good allergy to a peanut, for instance, your chance of reacting to another legume is higher. If you have a tree nuts, fish, or shellfish allergy, there would be a chance of a reaction to another similar food in those categories which would be 40% or higher. So typically, unless the person has testing to show they are negative to some of these fit, they are generally told to avoid all classes of that food. So the question now comes if you start having not maybe a major food allergy but in the same category as a legume here, I will push and should not be talking about, this is a food where at least there's a 30% cross risk of people with peanut allergy. Is certainly influence the European Union to add it to the list of allergens because Lupin can also be an allergen in and of itself. So what is the cross-reactive potential that we need to worry about with these new foods?

I think it is important to mention that we will have a talk on prevention but also after this qualified health claim, we start to see a lot of products that are coming on the market with catering to an infant population and catering a low level now of allergen exposure will maybe help them achieve tolerance and avoid [inaudible] individual threshold is my threshold. What will I react to when I encounter it? In some districts, somebody's individual threshold can impact risk management decisions. If you have a child in school who is severely allergic, that school may have to take drastic measures to protect that one child. But so these are, you know, so and even from a public health perspective, unfortunate, if we make a decision on the threshold and somebody reacts less than that threshold, this makes news and we have to be aware. Analytical threshold is setting a limit of a test, yes or no, something like that, and regulatory thresholds have to meet our regulatory standards.

From a safety perspective in the center, we tend to want to know risk. But maybe there has to be a discussion about what is a tolerable risk here. It also implies some level of understanding severity of response as well. Until now, there is no threshold defined by FALCPA for FDA. Because of this, the FDA act, when the law came out, developed this document to identify viable approaches if we were to determine a threshold. And these were the three that were viable, the analytical-based approach, we already talked about it, setting a level, determining if something like sulfites, if it is above a certain level, you label it. These are some of the allergens that we have. The safety assessment-based approaches the typical approach used by the evaluation of food additives. You study the doses to determine LOAEL levels and use safety factors to extrapolate from that data to go to human data to develop a safe dose. With regard to allergens, this is a challenge because there's a lot of data already from human studies. And many of these might be the most sensitive individuals already. So do you add additional safety factors and is that becoming too conservative and maybe not practical? The risk assessment-based approach was believed to be the most robust method to determine risk in relation to dose. This requires a lot of data. What this method can do is doing something like determining what this dose distribution, what is the dose that causes 5% of the reaction to react to or 20%, and so it gives information. This is what process initiatives such as the voluntary incidental trace allergen labeling which will hear more about later is using as an approach. In this area, the expert panel has determined references which they believe can be used to determine when you put an advisory label on.

One of the limitations is this is that I am showing you here, it's not based necessarily on severe doses. So if we wanted to understand a little bit more about severe, went to get that information. This is on population eliciting dose severity. They found that none of these individuals tolerated this dose and maybe the actual number of individuals reacting to that was last, maybe even 2%. This did not have a placebo arm and may not be the most robust, valid study. But it does show some information that there is a dose that is tolerated.

We did an FDA study based on eliciting dose thresholds to link to a severe symptom. Some studies give you what the eliciting dose is in what the symptom is. Based on the symptoms, we determined whether that was a mild, moderate, or severe reaction. There are three curves based on mild, moderate, and severe symptoms based on the eliciting dose. And for peanut, you see that the lines are different. There is a significant difference. That means every subsequent lower dose you have a milder reaction. Is this an effect specific to peanuts or others? We will see. We will get a lot of information as more of these studies are done.

Thresholds are important in allergen hazard. Recall scenarios help us determine the need for recall and determine the hazard class of recall. There's reasonable probability. These are based on probabilities you can use population estimation data to help. We have started on a case-by-case basis and making determinations of some recall scenarios less than a class I hazard.

And the last two slides, this is my disclaimer slide. This is, I think threshold could have an important role also in cross contact and preventive controls. One of the, is did not establish thresholds, it also does not require testing for validation. So valid industry concern is how clean is clean from an allergen standpoint. Also, advisory statements, as I told you, are not required. They are voluntary picked the decision to put an advisory statement on it is also not something that regulatory agencies are here to answer. Having a threshold may help in for these decisions and also provide more transparent allergen information. VITAL is one. The benefit is it gives you a yes/no when you need to put an advisory statement in. Products that have an advisory statement much higher levels of allergen than products that do not have a lot of allergen in there, we know that, like I said with our chocolates, there are higher risk products. So this may

be a good time when we are having companies look at preventive controls to try to understand a little better which products have higher or lower risks and maybe matching those products with specific labels.

And then my last slide is, if we do establish thresholds that have to have a public outreach component, we can put out a request for comments, 405 submissions to docket, and what we found is that [inaudible] Establish thresholds because again could be just education or fear. But they have a loud voice. If we do embark on this, we have to develop outreach to educate consumers and clinicians about thresholds and reactivity risks. And if we do, it should be based on good data and is practical and enforceable. Thank you for your attention.

Taylor: We will have a discussion session [inaudible]

Audience Question: [inaudible]

Luccioli: The question is how variable are these with ethnicity and so forth. Very good question. There are studies that would suggest that African-Americans in particular might be at higher risk for some types of reactions, allergies, especially crustacean allergies. But I would say the data varied from different populations. Some also suggest that East Asian populations coming in are also developing more allergies more rapidly than the existing population in those particular communities. So it is interesting. So communities, maybe in their own communities back in Asia, there's not a very high incidence of allergies. But when they are transplanted into Western countries, they tend to have a higher rate, a high rate, but maybe an accelerated rate of allergies compared to the people who are in a population. So it is an interesting time when we are looking at those factors.

I think maybe we should, there's one more question? Yes.

Audience Question: Thank you for the interesting topic one label that confounds me is the parent of child of allergies, it says this product was manufactured in a facility that also potentially processes tree nuts or milk and so on but it does not list that in the ingredients and I don't know how to interpret that from a risk perspective. Do I not buy it? What is your take on that?

Luccioli: We will hopefully have a better discussion about that later. That is a very valid concern. And I think, what I can tell you is that, unfortunately, the type of advisory statement, even from the dark chocolate study that we found, they looked at even type of advisory statement at this on a different in terms of statement and levels of allergens. So that statement that you see there could have as much of a risk compared to a may contain statement potentially. We do not know. It's interesting because of people say I always stay away from may contain. It's obvious. But these other statements, they think there is a difference in terms of risk. And that is a challenge, I think that is where maybe I think we could make some improvement on time products with a type of risk because we know that consumers want to consumer products. They are unhappy that they cannot and they want to eat it. And they try to rationalize why or why not they should eat it. So if we had better information about what that risk level is, I think that would help. So that is a good question. Thank you for that. And I will, with that, yes, we will move on and I have the pleasure of introducing the next speaker, Dr. Matthew Greenhawt. He is a board-certified allergist and pediatrician. He did his medical school at Columbia and his residency in allergy immunology allergy at University of Michigan. He is now the associate professor with the Department of Pediatrics in the Children's Hospital Colorado and University of Colorado School of Medicine. And he is the director for the Children's Hospital Colorado food challenge and research unit. Thank you.

Clinical Management of Food-Allergic Patients: Prevention and Treatment--Where Do We Stand?

Matthew Greenhawt, Colorado Children's Hospital, Denver, CO

Good morning. Thank you very much for inviting me to talk. I will go over some of the clinical aspects to sort of follow-up on a lot of what was just presented. These are my disclosures. I will pause for a second.

So as a clinical doctor seeing patients and doing research, a lot of my research has been in between the gaps, understanding the human response to the allergy epidemic. One of the things we are grouped with is, on one hand, we are to treat at your food allergy and do it as fast as we can. We also need to understand that not everybody, with every pharmaceutical solution to a disease, there's always going to be some people who do not benefit. So, we need to learn how to maximize how they can live the best life they have with food allergies.

When we look at the choice between treatment and avoidance, this is a completely new paradigm. When I started in allergy in 2006, we were just looking at things that might be able to, early-stage, phase I, phase II, that might potentially treat a food allergy. So, I was brought up in an era where it was strict avoidance and if we could move that needle, it would be fantastic. Now my fellows we are training, they are looking at potential of a couple of solutions that hopefully will hit the market within the next year to 18 months. And that is a whole new paradigm which is wonderful. So, this is a fantastic time to be in the field. What we have to advise our caregivers are that they are really faced with multiple decisions. And to treat or continue to avoid is really the fork in the road they will come to. When I think about what the benefits might be, they can about perceived benefit of the therapy versus the risk of accidental fatality. Is much lower than is commonly cited. It's on the level of lightning strike. That still may not sort of resonate with somebody if they are still focusing on I could still get stuck with this reactivity.

But overall, it is still there. People might prefer to avoid therapy that over burdens their life. These kids have to go to school, they have soccer practice, they had piano lessons, whatever, they're kids. So, when we have a therapy, it has to fit within a lifestyle. It also has to be affordable. It has to have realistic expectations of what is going to happen. Some people might feel that doing something even though it is a partial or incomplete solution is better than doing nothing. These are all things that families have to deal with. As providers, we need to be able to define what our patients should have for expectations and goals. Really, we cannot judge or prescribe. It's not our job to instill our values on the patient. It's our job to clarify the values but we are more or less a spirit guide in terms of allowing them to come to a decision that makes sense to them. But to get to that point, we need to move the data about these therapies and choices they have. If we cannot inform our patients, then we are not doing our jobs.

There are two fast-tracked approaches to treatment. There is an oral solution and percutaneous solution. Will go through the publicly available data on this. The caveat is there are slight that's available on the websites and the manuscripts have not been published yet and I don't believe that either product has limited their formal application for approval.

This is a fairly old therapy. If you go to the 20th century, there are a number of papers talking about kids with eczema being re-fed their allergen with some success but then it dropped out and then it came back. This is equivalent to what we do with allergen therapy to a cat or ragweed. You are essentially giving slow, incremental doses trying to build up a level of

desensitization. That means a temporary transient state that is still dependent on receiving a certain dose of the allergen within the specific interval. If you do not meet the qualification, then your protection will wane. That's very different than what was mentioned earlier, sustained, unresponsiveness, which is more or less sort of the five-dollar word for cure or tolerance at this point. With desensitization, we know that from the early studies, this actually can happen for most patients. But it is hard to predict who is going to have the best effect. And it is very hard to predict who is going to have a more lasting or sustained effect. Part of the issue we are dealing with is a duration of therapy, optimal dose, and which allergens to work with. We know that milk, egg, peanut you can actively desensitize somebody. But things happen in the trials. Across the immunologic response, you see a few common things. You see the level of IgE against the food that comes up over the first 3 to 6 months and then you drop and go to the baseline and then you see this other antibody, IgE4 start to steadily decline over the first year of therapy and those tends to be the markers we define.

There are immune cells, things that change from allergic inflammation more towards infectious inflammation. But that effect has not been seen consistently across all of the studies. It's a little bit elusive exactly what happens. But we know something does happen and that's not really reassuring coming from a doctor. But the typical protocol for oral immunotherapy is that you start with an entry challenge pre-study. This is to define how much allergen you are reactive to. I know that the mantra is strict avoidance, even trace amounts can be dangerous. And while that has some validity to a certain extent, when you are looking at actively treating, especially for phase 2 and phase 3 trials, you need to know how much change is occurring. So, the studies are all required for entry food challenge for the parents don't like this one bit. The doctors do not like this one bit because these are kids that we know are allergic and it's not being done for diagnostic purposes and they're only been done so we know exactly what the threshold is. So, some of these do not actually go very well and they end up requiring epinephrine and other interventions. So, we challenge and figure out what the dose is that will provoke a reaction and they go through a rapid desensitization over the first day. The earlier study built up to 50 milligrams the newer studies are building up to 12 milligrams. These are very tiny amounts, but these are milligrams up in a protein. It's a fraction of the total weight.

Once we get them through the initial desensitization, they start to build up and double the dose every two weeks. They take a dose in the office, they are there for a couple of hours, and then they are sent home to repeat the dose and come back every two weeks. They are brought up to a maintenance level. The current product that just finished phase 3 is 300 milligram of peanut protein maintenance level and they are held there at this point indefinitely at least with the pharmacologic product that is going to be submitted. Other studies have looked at higher levels on the level of upwards of five grams in Israel. There are other U.S. studies. The studies at that point, once they hit the maintenance dose, you tend to see placebo group crossover and then you see an open label type of situation where they are looking at long-term effects. So that's the typical oral amino therapy protocol.

There's a company based in San Francisco that has user characterized peanut flour that is a capsule you pull apart and it is dropped into either applesauce or chocolate or vanilla pudding. It's mixed and the children eat that and that's how they take the dose. These are the phase 3 presentations topline data from the recently completed trial. For inclusion, they needed to tolerate no more than 43 milligrams of total protein. So, the challenge was done at one milligram, three milligrams, 10 milligrams, 30 milligrams, sorry, and they need to react before 100 milligrams. They were randomized 3 to 1 and built up to 300 milligrams over two weeks I just described. They were held there for six months and did an exit double-blind placebo-controlled challenge where the primary endpoint was a tolerance of 1.043 grams or they had to

tolerate at least 600 milligram doses. The main effect from 300 milligrams maintenance to 600 milligrams with no more than mild symptoms which is a whole different subtopic of how both companies defy their clinical endpoints and their challenge criteria. I will say that neither did it the same, so it makes it hard to compare the two products that we will talk about.

You can see some sample demographic. They specifically went after those who had some of the most severe reactions assuming that that is the population that needs the most protection. Most of these kids were multiply food allergic and highly sensitized. We had some of the highest level that we give her peanut specific IgE. All of them had a fairly low threshold to enter the trial. The median triggering dose was 10 milligrams which is 1/30 of a peanut. So it's not a lot. This worked very well. In the intention to treat population on the left, you see a percent of placebo responded versus 77% of the active group. That's over 60% absolute risk reduction and at some of the best that I have seen for an allergy study. Secondary endpoint was tolerance over 1000 milligrams. With that, they had very good endpoints as well, I am sorry, I read the wrong one, the first and fourth 600 was 67% and 4%. And the 1000 was 50% and 2% so it's a very strong number needed to treat. When you look at the protocol population, the results were even better. So this worked very well. It also worked well in the older group. But they are focusing on ages 4 to 17. That's where the initial approval we targeted.

Not only did it increase the amount of peanut you tolerate, but the reaction per milligram of peanut you ingested also was attenuated. You can see from the graph, you are looking at the top of the placebo group and the bottom is the active group and the red and yellow indicate more severe reactions and light green and dark green, the more mild reactions. What you can see is per target dose, after they completed therapy, when they did react at the severity [inaudible] parents of these kids a little bit more threshold that they can tolerate. When they do finally react, the reaction is less severe. You can see the number of doses of epinephrine required a difference between these two groups. Key findings, in active group, they developed fewer moderate and severe symptoms, they required more peanut to get symptoms, they were far more likely to complete a challenge, you needed less epinephrine. The clinical allergist, we can achieve these intricate, that would be fantastic.

Safety was good. Oral immunotherapy has never shed light on the high rate of discontinuation. In this trial, 20.4% of the total population dropped out. That number has been consistent across all the studies. This is the largest oral immunotherapy study done to date some earlier studies had less than 50 kids but about the same level of dropout. The one issue that we had seen with oral immunotherapy across all agents that had been investigated had high gastrointestinal reactions. You take an allergen it's going right into the lining of the stomach, that's where the children tend to experience symptoms first. I can't say that for my own experience as an investigator in this trial. We do extinguish, but it takes a number of doses to get there before that smooths out. Before that point, a number of families discontinued. That is just the cost of doing business with oral immunotherapy to some degree. That can be improved by number of different ways. But it is a relatively fixed constraint that we are working on. There were anaphylaxis, 14.5% investigator reported reactions most of which were mild or moderate. But those are slightly more than the average reaction, so again, that is one of the other issues. One patient developed a related disease which is an allergic swallowing disorder. On the spectrum of IgE food allergies, it is distinct. It has very good efficacy. But it does have this safety profile.

Moving from the commercial trial in the U.S., this is a unique study that is being done and repeated in Australia. A group was using a novel form of peanut oral immunotherapy that was spiked with a probiotic. In an initial study, they show that patients who received the peanut oral immunotherapy plus probiotic, 26 out of 29 were desensitized. Of these 23 out of 28 patients

after they stopped the therapy for two weeks, still maintained in effect which was fairly interesting. There were some design problems. A lot of it was a relic of when they started this therapy. The initial therapy has gotten more safety in mind and they did not want to challenge certain kids and they did not have to. Was one of the knocks on the study. Anyway, the probiotic was equivalent of about 20 tubs of yogurt so it's not something you can easily replicate at home. They followed 48 of the original 56 participants over 4 years after they stopped therapy. They were able to track 24 in the PPOIT group and 24 in the placebo patient after the exit food challenge but there was no set protocol for what they could do. They were basically encouraged to eat as much or as little as they wanted, and they were followed for 4 years. There was no set protocol. They were then brought back in and told to intentionally stop eating any form of peanut for eight weeks and repeated the challenge.

What they found here was that 16 of the 24 subjects versus only 1 of the 24 placebo subjects were regularly ingesting peanut ad libitum. Could see a poor natural history for those still allergic in the placebo group. But it was a fairly good follow-up of those in the PPOIT group eating peanuts. The amounts were variable. The target they were looking for was about two grams a week. And you can see that a lot of these kids were not eating that much peanut at all. 16 out of 20 were eating it regularly and others were reporting no reaction since stopping the therapy. They were able to get a smaller proportion to agree to the eight weeks. Imagine you are doing fine and eating peanut for 4 years and that you have the investigator that calls up and says stop for two months and see what happens. It's not necessarily a big selling point. But they were able to get some of these kids to come back and do it and they found that seven out of 12 kids went to the challenge on the PPOIT group versus one out of 15 were able to stop for eight weeks and tolerate the challenge and eat as much or as little peanut as they wanted.

What appealed to me was not the study design. There were plenty, but the target, this is what we want, we want the kids to have a normal eating pattern. Both of my kids are not peanut allergic. But they don't necessarily eat two or three grams a week. To eat it intermittently and that was how we would define tolerance with the applications of this study, if you can be replicated, they are doing a trial in Australia, is that this might be what really moves the needle on what we can offer parents, not can you take something 300 milligrams or 800 milligrams every day for the rest of your child's foreseeable life. Can you actually get them back to a normal eating pattern? That is what makes this study so important.

There are a number of other published studies on oral immunotherapy. You can see from the fourth column, the size of these have been fairly small. Most of these have been studied in children, the dose and duration, you are getting the same type of outcomes. You can effectively desensitize these kids. The question is where do you go and how do you predict who is the best candidate. And that is really where we have not found any markers or other clues. It makes it a little bit frustrating. But it's still offering something to those parents might be interested in that.

With egg and milk, there is less data. Milk is hard. The data from Johns Hopkins has been that the allergy tends to come back, and a lot of these kids will get up to a cup of milk but then they develop G.I. pain and they will stop and it will go back to avoidance which is interesting. With egg, this has been minimally described. You could get kids desensitized on egg and if there was some minimal sustainable response, peanut has been the one that has been the major focus. And I think milk and egg will pick up now that peanut has got a lot of momentum.

Predicting symptoms from oral immunotherapy has been a little bit of an issue. It's known that these kids will have some symptoms. But it has been considered relatively safe and effective. This is a number of the earlier peanut studies that have been grouped together looking at

predictors of overall adverse events, adverse events that occurred build up and maintenance. There aren't a lot of significant predictors. The one that was the most surprising was that allergic rhinitis seems to be a fairly good predictor in all stages. But things that we would expect is asthma, eczema, really were not predictors, the only thing to potentially predict overall rates were the size of the skin test, larger skin test maybe giving a little bit more but that was not consistently seen in the maintenance. Again, we are looking at a range of symptoms.

What they found, they needed to treat the symptoms. On the left are the actual medications used, a lot of antihistamines, some albuterol, some steroids. What concerns me here is where they start to look at things like respiratory symptoms where there seems to be a lot less epinephrine given than the guidelines for anaphylaxis management would suggest. These are investigators watching these kids carefully at their discretion and guidelines and what you do in practice might conflict. But again, these kids get coughing, wheezing, highs, abdominal pain, vomiting. So, there is a little bit of a cost doing business with this type of therapy but the effect is very, very good. That represents the potential trade-off for parents to think about, we have a lot of medicines, some things have more side effects and some things have better efficacy than others. We have to make sure it's reasonably safe. But it's not our decision as a provider to guide someone to one thing. That's more the parent or patient choice.

This is the other side of the coin. This is a system that is applied, the allergen is sprayed onto a patch that is one on the skin. It targets the immune system in a related but different way. This is a proprietary technology unlike oral immunotherapy which uses essentially what is called by some grocery products, this is a special patch developed by a specific company. It has shown pretty good efficacy, slightly different measuring scale, but the biggest selling point is the rate of side effects is very low. There are two trials, one just finished another one ongoing, and they note that most of the children wearing the patch will predictably get some sort of irritation around patch site. But very few other systemic side effects were seen. This can induce a very good immunologic change, a master cell that sort of controls other chemicals that help propagate an allergic reaction, those tended to decrease. And there were no associated [inaudible] non-oral route of exposure. The phase 3 trial for peanut showed significant effect at 250 microgram dose. The milk had 250 micrograms as well.

The phase 3 trial for peanut was conducted in 31 centers across five countries, randomized 2 to 1. The patch is worn 24 hours a day and changed once a day. These are also highly allergic patients. You had to have a fairly big skin test and you also then needed to fail your entry for challenge below a certain level. Again, we are looking for a dose-response. It would have been nice if they had used the same scale because it would have made it easier to compare the two. But they used different levels at the food challenge. They stratified this into a low and high responder group. So, if you had a dose defined as an objective that triggered the reaction, if you were less than or equal to 10 milligram, you needed to have an exit challenge of 300 milligrams or greater and if you are over the 10 milligrams, then you needed to go to 1000.

The entry characteristics, the median dose in this trial was a bit higher than what was reported its different characteristics, so it is very hard to compare. The same type of population, a lot of patients with asthma, dermatitis, multiple food allergies, so we were looking in the same population. What they found was that 13.6% placebo patient hit the primary endpoint versus 35.3% of their active treatment group. That is the number needed to treat at 4.6. It's a reduced effect compared to the other therapy. There was a little bit of reporting convention here. As part of the statistical analysis plan, they were asked by the FDA to also meet an endpoint with a lower bound of the confidence interval on the active dose was not supposed to cross 50% and it just did. The lower bound was 12.4%. This has a very good safety profile. There was only 1.1%

of dropouts. There was high compliance. Most of the adverse events were skin related where the patch was. They were mild-to-moderate. And 95% completed the trial which is very good.

The cumulative reactive dose of the total amount if you add up all the doses that would tolerate in a challenge that shifted upward with an immediate increase which we will explain that number in a later presentation. When they looked at this, so the trial was a one-year study. You can probably only randomize for only a year you can do it longer, but it is difficult and there are points against that. When you look at the label follow-up, this is the phase 2 data, there were different responder rates. But the purpose was to show what happens when you wear this patch for longer than one year. What you can see is that the number of patients meeting the responder criteria increased. By the end of year 2, it went up to 80% and then 83% at the end of year 3. On the right, what you can see is an increase, steady increase in the median from 44 milligrams at the baseline of the open label study when it started then up to 1.4 grams by the end of year one and year 2. This is a little bit of slower burn. I like to cook. You can flash my something and it can be ready quick we can throw something in a crockpot and it takes a little longer. But at the end of the day, you have a nice meal. And this is just a different immunologic route that maybe does not take it there in a year or does not reach its peak effect in a year. This does show efficacy. Open label studies in phase 3, you have to be a little careful, but the trends are promising if that can be replicated. The end of year 3 for these patients is starting in February. We were the first U.S. site randomized so we will start the challenges at that point. Hopefully, there will be open label follow-up for the data coming out soon.

This is the milk study and dose range. This worked pretty well, and we are getting short on time, the patch was the most efficacious. They had 57.9% respond versus placebo rate of 32.5%. You will notice the placebo rate is almost 3 times what you saw in peanut. The natural history is different. This is a moving target. You are fighting history at the same time you're trying to treat. There is still a pretty good absolute risk reduction, and this will enter phase 3 soon and has similar safety to the peanut.

When we looked at what motivates parents to seek therapy, what we found were some interesting characteristics. This is a 22-patient study and part of my funded grant looking at comparative effectiveness of food allergy therapy. We wanted to know what the motivators were. And we looked at our trial patients from both groups and what we found was that parents were really seeking not necessarily a peak dose, but they want a buffer. They want something that will provide minimum protection with minimum risk. It was described as a buffer. It was described as a fully knowing that they are not looking for a cure. They are just looking for something to take the edge off.

What parents are looking for might not be that huge increase. What they are looking for is something more personalized. Once they achieve that buffer, it will have a meaningful impact on quality of life. However, most of the parents informed us that they are going to go right on avoiding and being vigilant, but they will feel more comfortable about their practices and making the child feel safer with a buffer. It's an interesting psychology behind what this might translate to. The way I see it is they are so used to being told one might be very dangerous for you this could be very dangerous, and we need to move them to a viewpoint now where you can actually expect your child to get better. And I think once they understand that the child can get better, maybe they will start to have greater aspirations for what better might mean for them. So baby steps are along the way. But this certainly makes life better and I think the answer that they gave us about this threshold is well aligned with what both products are designed to do. It low-dose desensitization. That seems to be what the parents are telling us.

Quality of life can be fairly bad in food allergies. There's a lot of fear of accidental reaction, hidden ingredients, inability to deal with the consequences of reaction, fear of death, social stigma, or whatnot. There's also high economic cost of food allergy. We cannot predict the severity very well. That leads to differential quality-of-life. This looks at a large population of food allergic individuals both from self-reported means and from our clinic diagnosis. What you can see is that it is a heterogeneous population, so there's not one food allergic population this is heavily segmented into different aspects. While our clinic patients tended to have better quality of life, different people may seek different things. Depending on who we listen to and who the stakeholders are, we may be motivated to go for different solutions.

Maybe some of the people who do not have the access we are not hearing from. We cannot presume there is one desire or one need amongst this population. That's got to be carefully considered when we design treatment.

Quality of life can shift in oral immunotherapy and has not been studied robustly. It will go up to some degree. Although, when you look at the study, the fourth bullet point, they found different domains in different people shifted, which is probably not unexpected. But we need a better index to look at this. Right now, we measure the parent's impression of the child's quality of life. That's one thing. The children are too young to reliably report quality of life to some degree, but maybe we should be asking the parents what they want. It's a fair question to ask when dealing with pediatric therapy, something like food allergy, are we treating the parent? Treating the child? Or are we treating the spillover effects of what the parent interprets the child's illness to be?

I am going to quickly move on because we are short on time. Prevention, before 2000 we did not talk about deliberately or restricting deliberately for allergy. In the year 2000 the American Academy of Pediatrics published something that suggested that removal of certain high-risk allergens may be protected if you had you had a family history of allergy. 2008 that was reversed but no active guidance was published. It did not tell you when to introduce anything. In the last three years the guidelines now are starting to say, you need to do this and this at this frequency to help prevent. This is a very busy table of all the major prevention trials. There have been five studies that have investigated eggs, and two that have investigated peanuts. When you look at the sum of data, this is meta-analysis published in JAMA two years ago. The pooled data indicates there is a risk of effect for both early peanuts and early egg introduction, the different effects you can see the light green diamond shows a much wider than some. Some of the egg trials did not work as well as the others but when but when you put the data in it's a clear effect. Nothing so far from milk showing protective. Not risk reducing effect for egg was 44% lower risk, 24 cases per 1000 children. Peanut 71%, 18 cases in 1000 children. That's pretty good evidence that maybe the timing is better to do early than to delay.

This is the reported data from the LEAP study showing that when they looked at the kids that [inaudible] peanut early that there was a significant reducing effect. The effect was different based on if you had three markers of having a positive peanut allergy, the skin test positive kids receive more benefit than the skin test negative kids. Treatment were low overall [inaudible] given early to prevent one case, which is not bad given what we see in other drugs. This worked very well and was not a temporary effect.

These are the guidelines now. These are confusing. I am an author on this. We were confused but this was the best we could do at the time. [Inaudible] are the ones being targeted as high-risk for peanut allergy. There are strongly considered to be seen by an allergist or Specialist who can do allergy testing to test if there is no marker for allergy, if they are comfortable with

that or in the office. Anybody with a marker below about eight millimeters of skin test will undergo challenge in the office. Over eight-millimeter probability is likely they are already allergic so it's at the provider's discretion if they want to challenge at that point. Kids with mild to moderate eczema, no eczema or no family history are considered lower risk group. Introduction can be done around six months or in accordance to family's preference. It's really two addendums here but separated out as 3.

This is being implemented and different than what it said in Australia/New Zealand and in United Kingdom where they are saying give it around six months, not before four months and not recommending any testing. It's another conversation for another day why the guidelines differ from two other countries. The message is consistent in several countries, giving it early and it should have a preventative effect. It might not be the only issue in terms of the timing of introduction. There is some evidence how many foods you give early may also have an input on [inaudible]. More of the foods given early on might really be the more tolerizing effect as opposed to one specific food. There have been no randomized trials but these are all European observational cohorts where they looked and asked did you feed your kid fish, egg, or whatnot. Seems more food given early, the better the children did. Something to think about. It would be nice if we had the introductory trials looking at that but would be hard to design.

In conclusion I apologize for going a little bit over. Multiple potential approaches to treat food allergy. [Inaudible] in the office I can say with confidence in one year to 18 months you can come back and likely do something about it. It's the first time I have been able to say that with confidence and that is wonderful. That was for peanut. Hopefully will get there with other allergens. Long-term efficacy still needs to be proven. These are relatively safe, and I think we can go forward. This should help with quality of life, but there are a lot of very complex decisions to be made in terms of who is the right person to enter into therapy. Back in 2008 I had a [inaudible] came along called an iPhone. It was the first generation of iPhone enough to make me switch from what I was comfortable with, the Blackberry. Over time Blackberry's gone and most people have an iPhone. There are early adoptive and there are late adopters and that might be what you see. The technology will only get better. With those hopefully we can take the number of kids that need to be treated off the table through prevention strategies. This will reduce the risk, it will not outright prevent every single case, but people need to understand that. This is relative to one strategy. Another strategy will reduce the risk of developing allergies. Nothing is an absolute. It might not be just timing but the number of foods. There are lots of things to look at going forward. Thank you.

Taylor: [Inaudible] Thank you. Sorry. Too much technology for an old guy like me. I like to introduce the next speaker, my colleague, Joe Baumert.

We are going to take a 15-minute break. Or a 20-minute break. We will come back at 10:25 where I will introduce the next speaker.

I think we need to move along in the interest of time. Now, I will introduce our new speaker, my colleague, Joe Baumert. He is Associate Professor in the Department of Food Science and Technology at the University of Nebraska and serves as co-director of the Food Allergy Research and Resource Program. Joe got his degree from University of Nebraska but did PhD in area of food allergies. Before that he was trained in meat sciences. We made sure that he finally saw the light. Joe has developed a very active research and industry outreach program in the area of Food Allergies. He is interested in some things he will not talk about today like the digestive stability of allergenic proteins, and the development improvement of analytical methods, but both of us are very interested in structural doses and quantity risk assessment.

Joe has really pioneered the development of the risk assessment approach. He is going to talk to you on How Much Is Too Much? Threshold Dose for Allergenic Foods. Joe?

How Much Is Too Much? Threshold Dose for Allergenic Foods Joseph Baumert, University of Nebraska, Lincoln, NE

It's a pleasure, and I appreciate the invitation from the organizers for the opportunity today to talk about this. As we think about a lot of the individual threshold data that has been coming out from various studies, such as the one Matthew had talked about, we can then put that into a context looking at it on more of a population basis for purposes of risk assessment and applications, which I will talk about later in the presentation. I want to set the frame for where we are at in the process of looking at that, modeling that data from a statistical basis. Stefano Luccioli did a nice introduction for a lot of that. We will dive a little deeper into the statistics that underpin some of those distributions, as well as reference dose we will also talk about.

Again, I appreciate the background that has already been provided. By way of more of a disclosure, or rather conflict of interest, I work at the University of Nebraska and our Food Allergy Research and Resource Program is a consortium of industry funded by the food industry and others. We have about 105 member companies that help support our research and outreach activities. We do get royalties for licensing that goes on for development of the Neogen Corporation test methods for analysis. I consult with DBV and I am a member of the VITAL scientific expert panel and the [inaudible] threshold action levels expert group, which you will hear about at the end also.

We look at thresholds and we think about the evolution of the process that we have looked at for food allergy, in general, I would say back in say back in the early 90s, maybe even 2000s there was little data collected in regards to clinical dose-response. That dose for that individual. Really what is not assembled in any way that we could begin to look at that on a population basis. We are still grasping the idea of whether or not allergens really follow the Classic toxicological approach, in which for those type of risk approaches animal models are primarily utilized. With food allergy, we see very little correlation between animal models to a human response. There are challenges and we relied on using the clinical data from the human population that is allergic.

The other key area and key question at the time, do all allergic reactions occur at very small exposure doses? Adding to that, do the small minute traces cause severe or fatal type responses? Again that was the dogma that carried through for several years. Again, we will look at more data to answer some of those key questions.

In the mid-2000s, there were several working groups that looked at different approaches for risk assessment that could be utilized for analysis of allergen exposures. Two key Working Groups would be the EuroPrevall study that was a European framework commissioned project that was ongoing in mid to late 2000s that looked at some of the different data in regards to different approaches for looking at allergen risk assessment. ILSI-EU was part of the group as well as the UK FSA. Safety approaches, analytical approaches, benchmark dose, margin of exposure, and more advanced quantitative approaches for risk assessment. With that, again, they concluded that the benchmark approaches and [inaudible] approaches provided the most robust form of allergen risk assessment, but was there sufficient data to be utilized at that time for the analysis? Again, you will need to utilize distribution for the population analysis. At that point in time, that was kind of a charge for the industry. Academic groups really looked at what data was

available to begin to assemble that data. 2006 FDA threshold working group also looked at similar approaches and arrived at that quantitative or risk-based approach as the key for allergen risk assessment, so to begin alignment between the various independent Working Groups.

Food allergen thresholds has evolved in the science that we have utilized to look at that taking the individual data on through to looking at population dose distribution. That data does exist for a variety of different studies that have been conducted clinically, whether those are oral challenges conducted for diagnostic purposes, threshold trials, immunotherapy studies, where we can utilize that baseline for introductory threshold analysis for those individual data points to establish those reactive doses for each individual. We do have emerging and continuing to gather more information of threshold doses that can be statistically modeled to look at what the population looks like. And you can see several different distributions similar to the one I provided here for peanut. Again, you see a wide distribution of individuals within the population. What is amazing with food allergies is that you see several orders of magnitude difference between the most sensitive individuals that Stefano Luccioli commented on, to those that are allergic where dose is required a probably several grams of material before they react. So again, we can utilize this data to look at applications we will talk about later.

How do we model that data? What are some of the key criteria used for this type of analysis? The analysis that we conducted has looked at underpinning the objective response. We are looking at, again, the last bullet point where we looked at objective symptoms for establishment of that NOAEL or LOAEL value, in the reactive dose in the dosing schema that Stefano had showed as an illustration earlier. Again, we're looking at gleaning data from either published studies, published clinical data available also for participants for clinical groups that are willing to participate in this type of analysis. Similar to what Stefano Luccioli mentioned, the key criteria we look at would be history, as well as looking at skin prick test positive patients, or serological positive patients also. Again, from these different studies we can establish the NOAEL or [inaudible] for each individual.

Statistical methods such as a interval-censoring survival analysis I will not dive deep into the statistic. Think about a dosing schema where reactions occur, for example of this one where we have a dosing scheme going up to 500 milligrams, you know that an individual will react for example, it subject two, which has not established reactive point at 150 milligrams. That individual tolerated the dose of ten milligrams. The dose at 50 milligrams, and then reacted at the dose of 150 milligrams. If you think about how that dosing scheme works, we have a reaction to a dose probably similar in-between 50 and 150, but we are not exactly going exactly going to titrate individual doses milligram by milligram to evaluate where that reaction may occur. Interval censoring survival analysis allows equal probability between 50 and 150 milligrams to evaluate that type of response. Subject two would be what we call interval censoring. Again, that has an established reactive dose for LOAEL, as well as NOAEL value. We do have individuals dependent on study design. They may have started at a higher dose say, ten milligrams, in this case, in which we had subject one, and that subject reacted at that first dose. We know they have a LOAEL value but not sure where that NOAEL value is. Somewhere between zero and ten in this case. We apply those equal probabilities between those. Subject three is an individual with a positive history of response, as well as one who had gone to the challenge study. They have had maybe subjective responsive and application, but never had that object of response. In this case, we can establish a NOAEL of 500-milligram. The challenge didn't continue far enough to establish the objective endpoint. So again, we can then apply right censoring in which we would have basically a LOAEL out to infinity.

Then taking that data we can look at utilizing different programs such as [inaudible] or other packages that can look at modeling that using various parametric models. Three that are commonly used are Log-Normal, Log-Logistic, and Weibull distributions. Right now, one method over another we look at each of those different methods in our traditional approach. I will show you some new statistical approaches, which we can look at utilizing others in an additional statistical modeling method. With that we model that distribution and begin to look at estimating doses, or ED values for the dose values for that population. We look at that on the basis of discrete doses as I showed you before, ten, 50, 100, 500, are discrete doses. We can look at cumulative dosing also as we go to the process, similar to what Stefano Luccioli indicated.

With that within establish different eliciting doses. ED₁₀ for peanuts in this case based on 750 individuals would be 3.8 milligrams of peanut protein based off of the dose distribution modeling. Again, ED is just for illustration. We'll talk about reference doses later we wouldn't base necessarily off of the dose we were predict 10% of the population to react at.

Again, important to look at each of the doses, or each of the allergens individually, because not all allergens are created equal as I mentioned here. What you see in this graph is the different dose distributions for egg, peanut, hazelnut, sesame, milk, soy flour on protein basis. Important to note the protein basis rather than commodity basis. We see here several clustered together but there are a few that seem to be less potent, for example. With soybean shifted to the right, in which we see a less potent population distribution than what we see for some of the others such as egg and peanut, for example. Important to look at look at each allergen individually.

Our group, along with the group in the Netherlands has worked extensively to try to collect various data points accessible from those published reports, or clinical manuscripts, as well as working with individual clinicians to glean data from different clinical documents, or files. Again, we had a point in 2010 and 2011 where we collected various data that went on to underpin the reference doses for VITAL L. We will talk more about that more about that in a moment. From that point we continued to look for to look for additional data points. For example, for peanut we had about 744 individuals for VITAL analysis. Additional data currently would be about 563. We have around 1196 individual data points to model. Again, we did gain additional data for several of the allergens, but there is going to be some allergens that just because of the low prevalence we would never expect to get to the levels that we have seen for milk, egg, peanut. A good example of that would be soybean such as Lupin mustard allergy, limited number of individuals out there that have participated in these type of studies, and very low prevalence in the population in general. There are additional data points out there from various studies ongoing. Immunotherapy studies, I think, where we have some of that baseline data could provide additional data to look at also for various populations.

I want to put this in context for what we are talking when we talk these doses. I think this slide illustrates what we talk about when we talk about the milligram doses, that individuals react to and reference doses later on. Some of our most sensitive peanut allergic individuals react to about 0.4 milligrams for peanut equivalent to 0.1 milligrams of peanut protein based on 25% protein. In peanuts, eliciting a dose for sensitive individuals. Based on those threshold distribution curves, you can have individuals curves, you can have individuals that still have the first objective response to around five milligrams of peanut, and again, individuals that could react to roughly 400 milligrams, give or take on peanut variety, that could be about be about one whole peanut based on a Spanish Virginia type peanut copper example.

Then by diversity of individuals that do react to peanuts, and we see this resonate with several other allergens. Again, the key question would be, the low doses that do elicit reactions, those

have been established, but do we have data to support the long-standing notion that these very low doses, sub milligram doses cause severe and fatal type reactions? With that challenge and question, we looked at what Stefano Luccioli talked about already and it mentioned, we looked at trying to validate the dose distribution, as well as establish what type of response we saw around the distribution. The peanut allergen threshold study, PATS often called, is now published in the Journal of Allergy and Clinical Immunology. Two key objectives to validate the statistical model for the population of peanut allergic individuals. With this we took the eliciting dose we predictive 5% of the population to ED five value, 1.5-milligram of peanut protein. That was challenged in, provided in a small cookie to 378 unselected consecutive peanut allergic patients in three different centers around the world. Cork, Ireland, Boston, Massachusetts, and Melbourne Australia.

Based on statistical modeling, trying to identify and validate the hypothesis, we would predict that if 375 individuals were to go to the challenge we had 5% of the individuals react based on the Pearson analysis. We would improve the hypothesis if we had 5% of the individuals react. The [inaudible] intervals will be between 3.1 and 7.8% of the population that would react. Again, we were looking at, we have slightly few individuals that were in the study. Some of the key criteria in how we were evaluating based off of the clinical study, the clinical staff were asked to record any physical or behavioral changes observed or self-reported during the oral food challenge. Again, we were looking at those objective criteria to assess a response. I provide the different objective criteria, and you can see that it is in our publication as well. A couple of key want to point out would be three or more concurrent, noncontact [inaudible] hives that persisted five minutes, such as angioedema, rhinoconjunctivitis, diarrhea, vomiting, anaphylaxis were also part of that. Again, you can see that in more detail in the publication.

Jumping to the results, we did have eight individuals that did meet the prefixed criteria for objective response in the study. All of these were very mild reactions. Four received medications. In this case it was antihistamines, Benadryl, and that was per that clinic study protocol. That was here in the U.S., that's any reaction required application of antihistamine. None of them received adrenaline or epinephrine during the study.

Looking at some of the different reactions that occurred in the eight individuals, again we had rhinoconjunctivitis, [inaudible]. Most significant type of response we saw in two individuals was a minor case of vomiting. Two of the individuals, urticaria, rhinorrhea and other individuals in the study. The clinical doctors involved indicated in their view these were very mild type responses.

With those eight individuals, we had 2.1% that did meet the predetermined objective risk criteria, which was slightly outside of the of the bounds of the 3.1% for lower limit and our predicted, in the statistical model. We did not quite validate the statistical model. Our model would seem to be a little more conservative, and some of the potential reasons for the difference here would be, perhaps, some of the selection bias towards more highly sensitive subjects used to model the dose distribution. And the individual threshold studies, some of those may have been, again, they were from referral clinics. They may have been from a slightly more sensitive population. Some of the criteria included for objective response in those individual studies, especially ones from publications, we were not always able to identify, for example, did they had three hives, or current for five minutes or more? Somewhat indicate hives, cough or sneeze, which are objective responses, but may have been a single hive or a single sneeze, which would not have met the criteria.

The dose distribution model seemed to be more conservative. We did base the dose of 1.5 milligrams on the Log-normal distribution rather than looking at the log-logistic or Weibull model.

The Weibull model tends to be much more conservative, usually shifts the curve to the left, meaning you will have predictive listing dose at much smaller amounts. With that had we used the Weibull, tenfold lower than what we see for the log-normal, we probably would have seen my prediction, no reaction in this case. Overall, the clinicians indicated that the process was quite safe with mild reactions. In the peanut single dose study, again, they found it was a useful way to try to, most useful way to help with very anxious patients and parents. The quality of life study indicated there was a significant increase in the quality of life just knowing that several of these individuals were not in that very [inaudible] profile. I think that is an important additional outcome that we found in this particular study, that knowledge was powerful enough for those individuals.

Moving on to some of the work we are currently doing, one of the key things we had we looked the derivation of reference doses from the dose distribution models was that the expert group, and this was part of the VITAL scientific Expert Panel. We again looked at those different distributions to try to derive those reference cases. In many cases we looked at a looked at a combination of log-normal, log-logistic, [inaudible] distribution. Some instances we may have utilized one single model. We may have used a couple of models for derivation of that final reference dose, which was around the eliciting dose of 1% of the population or ED one for things such as egg or hazelnut where we had significant amount of data, or lower of ED five value for the other allergens where we had less data.

One of the criticisms was there wasn't a direct value that you can derive based on a single statistical model. Again, we do not have the biological rationale to utilize one method, one distribution over another, but we can utilize a statistical approach of model averaging, which can take into account various distributions into an account for uncertainties in those different models when applied into a single average model. Again, you can look at combining knowledge of threshold distribution, a goodness of statistics and arrive at that model.

This is a slide Ben Remington put together. This illustrates nicely with the concept. And this concept we're looking at individual studies, for example, with individuals across those different studies. They all have different reactions. Some are right censored, some left centered, some interval censored throughout the process. We'll be looked at different dose distributions, again, you will get variability across the various distributions based on the different parameters within that statistical approach. With model averaging, we can then take those and account for the uncertainties within the study, as well as applying weights to the different dose distributions to arrive at a model average distribution, in this case.

We're working on that analysis with the group at TNO, as well as international collaboration with Experts such as Matthew Wheeler from NIOSH, and Kan Shao from Indiana University, real experts in this area of model averaging.

One of the differences we utilized based off analysis previously done was utilizing the interval censoring approach, which had not been applied to model averaging previously. Again, that allows us to account for the different uncertainties amongst the individuals, as well as using Bayesian style modeling averaging to look at uncertainties, and weighted averages across these different distributions based on the goodness of fit. Importantly, looking at study heterogeneity in the analysis. We can look at differences and account for differences in locations, protocols used, different individual studies, different clinicians, nurses, other objective endpoints that are different can be included in the average model. We looked at six different dose distribution models based on some of the recommendations provided in the 2014 document on thresholds.

As an example, here would be a Kaplan-Meier curve for example data in milk for which you are seeing the individual studies for each individual line, and then the model average across the middle with the [inaudible] applied. We are applying the analysis to look at all of those individual studies, and arrive at that individual model average, which the blackline in amongst the traditional approach of the Weibull, Log-Normal, Log-Logistic models. There is little difference between the different dose distributions and different statistical parameters used.

Here is an example of the different distributions used, Log-Gaussian, Log-Logistic, Weibull, Log-Double Exponential, Log-Gumbel. In this example we had more of the weight on the Weibull and the Log-Double Exponential parametric models in this case.

Moving forward, how do we utilize that data? I think Scott may talk about some different applications where utilizing threshold reference doses would be appropriate, and, certainly, would help with providing a benchmark by which we can say to Stefano Luccioli's example, how clean is clean enough for an example? There are current ongoing activities that are already utilizing this data in reference dose values. In 2007, the allergen Bureau of Australia and New Zealand released the first iteration of their VITAL program, voluntary incidental trace allergen labeling program. The goal was industry led initiative to try to limit the use of precautionary labeling that may contain process on, and any other derivation of that advisory precautionary statement. Again, they were looking at trying to establish a reference value by which you would decide cross sharing labeling would be appropriate to use or not use, and again, try to limit the use of unpackaged, pre-packaged food products. One of the major reasons in Australia about 80% to 90% of pre-packaged food products have one of these precautionary labels on them. As an allergic consumer it was difficult to try to go to the marketplace and try to find food products that were safe to eat.

Without that we see the consumer trends that are moving towards ignoring those statements and taking risk into their own hands. 2011 we work with the VITAL program, and the Expert Panel provided the analysis based on the TNO threshold distribution database, which looked at modeling the distribution for allergens, and then arriving at the various reference doses. Much earlier, we had based things such as peanut, milk, egg, hazelnut, on the ED one value, which was eliciting dose of one percentile of the population that has that allergen. That was in part through a discussion we had with the allergic patient group anaphylaxis Australia, and [inaudible] in discussions on where to apply that reference value. Again, we used the lower interval of ED five where we did not have enough statistically modeled and deride the ED one value. This has since been endorsed by ILSI-EU in the Task Force panel mentioned in the beginning and disclosures. That was a multi stakeholder panel where we had clinicians involved, academics, risk assessors, and patients, allergic patient organizations were also involved. Again, they endorsed this concept. Additionally, IFVAM, another European organization utilized the data for the risk modeling portion of that project. It's unofficially being utilized by public health agencies and several countries to evaluate where the might be unintended allergens present and determining whether that constitutes a case of hazard risk.

Additionally, there are proposals by several by several European countries such as the Dutch, Belgian, German authorities that proposed utilizing threshold distributions, and reference doses by utilizing different approaches in each of these different jurisdictions. They looking at perhaps using the ED one, or ED five in other cases, and again, it's not a harmonized approach to this process. I will note that there are in some ways thresholds available, but only in two countries, Japan and Switzerland. They are both established threshold values, one of which I consider probably appropriate, which would be the Japanese level of ten micrograms per gram a part per

million protein from that allergenic source that has been instituted since 2002. Switzerland does have a value that would be indicated, but it's 1000 micrograms part per gram or part per million from the food allergenic source, which I think is quite high in this instance, probably would not be appropriate for allergen risk as a benchmark dose for a reference value.

We also had single studies for peanuts that looked at utilizing single-dose studies to evaluate milk, a, hazelnut. We are still in the quandary of having the zero threshold or zero risk process and with that we're seeing challenges within the industry within consumers taking risk into their own hands. They see the use of precautionary statements and will try to assign values to those statements. In one of the recent publications that came out of 40% to 60% of individuals did ignore precautionary statements. Further we try to assess the risk and saw that certain statements they would adhere to such as may contain or not suit, suitable for that they would ignore much more readily but in reality, based off of surveys and analytical studies that looked at different products we had the same opportunity to find that allergen residue in those particular products. I think utilizing this data and moving forward with reference dose and benchmarks would provide assistance. With that I would like to acknowledge all the people that worked with us and we will proceed to the next individual.

Taylor: Please continue to prepare your questions for the discussion section. I want to indicate to the off-site participants can begin to send questions and as well. It would be good for you to do that during the next few minutes so we can have those questions at the beginning of the session. We will have a more productive discussion if some of you send your questions in now. I would like to introduce Scott Hegenbart. He is the manager of scientific affairs for Conagra Brands. He works in the food protection migratory affairs group and has been very active in the area of food allergens for several years. Scott has had a number of positions in both academia and industry over the years and he is going to give us a presentation on food industry perspective on managing food allergen risk.

Food Industry Perspective on Controlling the Risk

Scott Hegenbart, Conagra Brands, Omaha, NE

Thank you, Steve. Thank you all for being here. It is unusual for me to be behind a podium, but the way technology is set up I will be standing here for a while. I have a disclaimer. My presentation reflects my insights opinions and observations. Not necessarily my company's policies because I do to use information and examples from outside the company. I talked to my colleagues, so we have a broad range of information. The other thing I want to make sure we are clear on is conflict of interest. We make products of food allergens. Sometimes giving in industry perspective of managing food allergens that make sense, but I do have to disclose that.

Earlier we had a great overview on how allergen management evolved over the years. Prior to the Midshipman-1990s food manufacturers had not heard of food allergens much less how to manage them. Practices were very different, and things have evolved over the years. We have added manufacturing processes that a bit of data and now we have allergen preventive control, so it has changed a lot but since most of us here are not from the food industry we have a broad audience, I'm going to give an overview on how things have changed.

Allergen management takes place through several different parts of the food production process. You start out with product development, supply-chain management where we buy stuff from, material receiving where we receive materials and how they are handled, of any cross contact during processing, label and packaging controls and sanitation and changeover.

Allergen management has a role in all of those things. I will give you a little sense of how that has changed. This is not a comprehensive [inaudible] on food allergens. Over the next five minutes I'm going to give you a flavor of how things change.

In the olden days reality and management we use whatever is great for the product. If we had some components that would enhance the components we would use it. Flavor encapsulation. If you have a microwave food product you main A the favor so they do not get strained during the microwaving process. Some may include fish protein or egg protein. And might not be an expected ingredient in the product but back then it did not matter. In this day and age, we try to do innovation without adding unnecessary allergens and preferences in, probably do not add any and any we do have we want to minimize the number we use because it makes the production facilities crazy because their schedules are highly dependent on managing those allergens. In the old days you order whatever ingredient you want. Usually the ingredient declaration was enough disclosure. You are telling us what is in there. Now it is different. Our specification has to have an allergen disclosure. This a separate document. We want to know that type of information because often times our customers want to know that information. Now we have third-party auditing schemes in addition to inspections from regulatory agencies where we have certain expected practices that will be invoked. Very different now.

Even something so simple as receiving the materials on the dock. Back when I first started the industry they arrived and got check to make sure reporter was correct and were stored where was most convenient. You notice here this list is a lot bigger than some of the other lists. Just the act of receiving and storing ingredients has changed dramatically over the years. We look at the actual ingredient statement to make sure it does not disclose allergens we're not expecting. We identify with clear markings. Often times it is color-coded or icons to know where allergens are, so they are moved to our facility in a knowing fashion. They are stored with appropriate segregation in designated warehouse areas. And some of my company' larger facilities we have a separate room where we store allergens away from non-allergen material. This is when they are on pallets wrapped up in boxes. Upon arrival, packaging materials we check to make sure the order is correct. We make sure the allergen information is correct. Printing errors happen. We will talk more about that later.

During processing, old practices bring out the ingredients weigh them watch the bats sheet and make sure we are putting the right ingredients. Mostly from equality perspective. We only pulled the ingredients we use at that time. Ingredients are still grouped by batch but there is a lot more effort to label them correctly and identify allergens, so people are aware that what they are handling is a potential food allergen risk. We want to make sure we do not misapply any allergens in a formula that does not contain them. Labeling and packaging control.

Pretty much all the packaging for the ship's in the warehouse. Simple verification on item code to make sure you are putting the right thing in, so the consumer does not complain they got the wrong flavor. The package may be on the line all day in the pool with the need. Things are impartial pallets. They may combine materials to save space. None of that is done. Only packaging for immediate use is brought to the line the item code is verified and packaging crosscheck on a timed basis. That crosscheck is recorded. Any unused packaging should go back to the warehouse and pallets are segregated. If you have one roll of packaging film, it gets a palette all to itself and the warehouse. We do not mix that up anymore.

Sanitation changeover. This is the area that has changed the most. It is an area that is most relatable. After you make your food in the kitchen you do the dishes. In the food industry the food production facility does the dishes. When finished with a product the equipment may have

been rinsed to make it clear before the next product is run. Sometimes introducing water is not desirable so you may scrape down any leftover material and run out some of the next product. In some facilities they will run the next product through. If that next product is orange and the previous product was white they will look to make sure that the color change is correct. A very simple changeover technique. Largely sanitation was determined by microbiological risk. Things has flipped with allergen management. And allergen containing product you will generally run it for an entire shift. When it is complete it triggers an all hands-on deck [inaudible] the production scheduling and sanitation process are determined by the allergen content of the product. What most companies do is make products that have no allergen. Then they change to one with egg and then egg and milk and when they are done with the most allergen containing product they chicken this process, so they can start all over with no allergens. It has changed how we do business in a food manufacturing facility.

Let's talk a little more about cleaning itself. We generally have a couple types. The most common is what cleaning. Where we cleared the equipment and disassemble it. Any excess is pre-rinsed. Foaming and scrubbing we use detergents that will break up proteins and carry them off and flush them away and then we rinse to make sure the material is there, and detergents are gone. And we sanitize. Dry-cleaning is the prerequisite to wet cleaning. There are some instances where you cannot introduce water. If you introduce water, you may introduce microbiological risk. You may have a situation you know chocolate can have milk in it. Chocolate handling equipment is double whammy. Hard to clean and you cannot introduce water. If you put water on melted chocolate, you will get a brick like glob that is hard to get cleaned. Sometimes we cannot use wet cleaning, so we clear and disassemble with dry-cleaning materials moved to scraping. Instead of rinsing we may push their and other material. Something like a salt and sugar to scrub out the material from the equipment. Then the detailed soil removal which may include industrial vacuums hand rushing or alcohol wipes. Do not be foldout alcohol does not break up allogenic proteins but in a dry-cleaning situation it gives us something that will volatile is off quickly while still having something damp to treat, clean equipment with. Very different now from scraping go in the old days. We have had a change in practice over the last 20 years.

Why do we take extreme measures? Because we knew that the reaction amounts were small, but we do not have an idea of how small they were. More is better. Initially the industry did not have simple allergen test methods. That was one reason we went the extra mile. Extreme practices are employed to account for this uncertainty and food allergen thresholds help add clarity. We will be talking a lot about that but there is a big perception problem with allergen thresholds. I'm going to go to some specifics. What is the fear? That the two companies we use threshold to stop cleaning and segregating entirely. If they do that cause contact is going to spiral out of control and myself or love ones will suffer potentially fatal allergic reactions. That is the perception. These folks and parents of children have very legitimate fears because they have seen their kids have serious reactions. In reality allergen thresholds are small amounts. Any regulatory reference doses are going to be smaller than that. Cleaning and segregation will still remain necessary. You're not going back to the days of scrape and go. You still have to clean. What action level can do is help us optimize our allergen management while supporting communication. We want to know how good is good enough and we want to communicate that effectively to consumers. Risk assessment helps guide resource application. Once we get some of this figured out which it will take years, there are other ways to use our time that will benefit the consumers. I will talk more about that later.

Let's get back to the subject of cleaning. How do we optimize that? We can use the surface lava lights as to see if the equipment is clean. We may use a CIP rinse water. Clean in place. The

equipment stays in place and it internally has a system that cleans it out. We can test the rinse water to see if there are allergens relating does remaining. ELISA results below the limit of limitation usually achievable. Create cleaning procedures optimize for the appropriate time and chemical use. Thresholds can help determine appropriate testing application. Not all allergens have a test available. Some food matrices resist testing. Some high-fat matrices it is hard to extract the allergen out. If you cannot get a positive control your test is not necessarily going to be valid. Certain processes meet testing impossible. I can assure you that we can get chicken chunks that have soy protein and we can test them in their chunk form and they will give us a positive result. If we put those into a suit it is invisible. It is like the soy protein is not there. That is another reason I was glad that FDA did not make validation a requirement under FMSA. Testing is not the solution to everything. Let's have a math minute. This is why I have the legal disclosure. How can we use threshold data to determine if it is clean enough if we cannot do a test? This is a tank. A crude illustration. How much milk protein is in the ingredient we use in this tank? 0.61%. It is used in a slurry at 5.8%. We have zero point. We have 0.03538%. This is how much slurry is in product eight -- and how much milk protein. This is a milk containing product. Let's go backwards. Let's take the serving size of that product which is a different flavor variety of another product. The action for milk is 0.1 mg. How much does it take to get to that level assuming that serving size? What I do is apply algebra. Solve for X here. How much slurry do we use in product B? How much of product A will have to carry over in product B? 2.78% is going to be a visible amount of material. If we emptied that tank and clean it to a visibly clean standard clearly that is sufficient. Now we have another case study for optimizing cleaning.

That last example we can look at the tank to see how much is in there. There is a problem, we have a lot of practices in the food industry where we cannot look. For example, a heat exchanger. We're going to pasteurize a product. A lot of piping. We cannot shrink employees down and send them to individually inspect the piping. If we could ocean might not like us to do that. Here's an example where testing might be our solution. Here we have to employ a double CIP process after using milk. We want to make a non-milk containing fruit punch after, so we test these CIP rinse water to make sure is clear of milk. Testing shows most milk protein removed during the program's preliminary rents. And we had it with [inaudible] then rinse again and sanitized. If the first rinse gets rid of our milk that is good. Instead of doing a double CIP process we can validate that a single CIP process is perfectly effective. CIP programs take four hours to run. If you do a double process that is an eight-hour change over time. Four hours is a lot of time back. Dry-cleaning, we cannot swab services because the allergens are sensitive, but we can test push their material. Remember I talked about sending salt three system to clear residuals. We can test that material. You can adjust that cleaning procedure or the amount of push through to optimize the effectiveness and efficiency. Below the test detection is not always attainable. If you have a situation where you have certain types of equipment you cannot necessarily clear it, so you have a clear test. Fresh old can help determine how much carryover represents the risk. Let's look at a large batch.

Two different allergens, milk and eggs. We have a product with a serving size of 114,000 mg. We have this much protein milk fairly small but even smaller for egg. Here's the percent carryover with the VITAL action carryover. Dispatch is 13,900 pounds. No carryover at the serving side is almost 100 pounds. If you are clearing that equipment and sending a push through and vacuuming residue out, you will see a larger pounds if you are vacuuming 100 pounds. So, we have a 250-pound mixer. Going to the same calculation. At a 250-pound mixer you will see the amount. If you're cleaning vacuuming and getting rid of the material, you should be fine. So, this changes things a lot.

We have third-party auditors. I call them the swarm zombies. They are thinking like microbiologist. Allergens are not microorganisms. They do not form biofilms. They are direct contact allergens and we need to think of them as a chemical hazard. For clear communication this is our opportunity we can use the knowledge we've gained to label products more clearly. We only have basic guidance. As mentioned, the regulations do not specify supplemental allergy labeling. The segregation process leaves many in the industry to creative labeling solutions. I have seen the product, it defeats the intent of the law by confusing consumers. It is not just consumers that can be confused, it can be suppliers of food manufacturers such as myself. If I didn't mention this specifically the allergens and food items have been changed to protect the guilty. The numbers are realist. They have been changed to protect the guilty and innocent.

Let's take a look of the supplier of [inaudible]. They have a validated imitation procedure that requires 90 minutes of downtime. That is a real number. For an hour changeover and they can do a validated clean and 90 minutes. That hurts relationships as I'm jealous. They use a contain soy statement on all products what do they do this, I do not know. One day they get a visit from FDA who says a contain statement should only be used if you have an ingredient there. They are using an actual contain statement to cover themselves. What did the company do? Did they change to a made contain statement because they have a validated cleaning procedure, or did they statement off? Their solution was to add a pinch of soy into every product they made. We did not have soy on our label. So, what are the implications? Allergens statements can be tricky. In this particular case, in that situation they must be truthful. Simply put a contain statement if there is no soaring that is not truthful. Their solution is to add a pinch of soy and that is misleading because you think there's a functional level of that ingredient in there. By the way, they have a good manufacturing process that is validate a bow. It turns out that after a lot of back and forth they do not want to take the 90 minutes. So, we told them to fix or schedule your making our product without soy first and whatever you do after that we do not care after you do your full clean that is where we want our product made. It is said that we have to have conversations. 20 years after we started doing this allergen management we still have to have these conversations. I find it frustrating. Managing allergens can make you pull your hair out. It is scary because it makes them think about their allergens. Clarity around the true risk, if we can do more risk assessment a gives them confidence that they are GMC's are effective. We do not have the same blind situation. We know how clean is achievable so let's use that information to communicate more clearly with consumers. This is one of my flights of fancy. This is not a regulation or a policy at any company, but it is a vision I have of how you might be able to use this type of data.

If you have a allergen that is not added or can detected there is no labeling necessary. And allergen that may be greater than the limited detection of a test but still below action level produced in a facility that handles X. Given allergen greater than the limited [inaudible] if the allergen level is greater than the limited detection consistently above the actual level and contains X from cross contact. Then if you add the allergen you have the contain statement. When I'm proposing is doing this type of risk assessment and testing we can have a spectrum that gives direction that consumers know what it means when it says a facility statement may contain. Also, this X from cross contact. You may see that on a few products but not many.

Thoughts on threshold. Clear consistent labeling. Disobeys regulatory action levels are a tool. They are not the ultimate thing, but they help us create the common language to communicate risk. Threshold based axle levels will not reduce allergen management. We will still have to do that, but it will change them. We will use validation to optimize sanitation to make it more efficient. We can do risk assessments to determine what label should say in targeting labeling.

Once we get that figured out we can increase regular, efforts for label verification. Why would we want to do that? That is my next section.

You can see here that over the course of the years, this ends in 2013. No one has done an update on this but they are using actual data from the food registry which is why it is called data. Notice allergens keep growing. Here in 2013 if you add Salmonella and listeria recalls they do not get as high as the allergen recalls. This trend has continued even though the date and. This data shows the root causes and cross contact wrong label or package, ingredient mislabel, terminology not correct. These are not cross contact type of things, but you can lump them together because they are all mislabeling misapplications. Keep in mind that these are the allergen preventive controls in the food monetization. I highlighted in red ensuring that we protected from allergen cross contact and label the finished food. It is a two-part game and most focus on cross contact and do not think about the labeling as much as they should if we look at cross contact 28 versus the number but let's take a look usually. If we take all of the mispackaging and mislabeling lump together and compared to cross contact at looks like a green Pac-Man. Mislabeling is one of our biggest issues. How can this happen? It is embarrassing in the food industry. We can't manage to get the right product in the right package. Let's take a look at a case study.

This was semi ripped from the headlines. Consumer complaints the company learn that the vegetarian juicy burger batteries has been packed into the savory burger patty packages. The juicy burger patties continual protein in the form of a cheese when the juicy burger and savory burger products only featured slight differences in packaging designs. Makes it harder for workers in the facility to make sure they have the right package when they have brand all the same. The plant appropriately schedules nonmilk patties before milk. The batch sheet shows the ingredient scaling in the staging was correct. Plant had thorough controls in place when changing over from milk to nonmilk products. What happens is nonmilk packaging was left on the machinery when the milk producing product begin production. They forgot to change it because they didn't think of it. We're so focus from changing to allergen and not allergen little things that could happen when changing from not allergen to allergen happen. That is what happened. The cheese blend had 15 1/2% protein used in the formula to give us .39%. Some poster for calculation. We have a 4-ounce serving size service product of the time we calculate that the VITAL action for milk is 434 mg of milk protein. The VITAL action level is .1. It only takes 25 mg of this product to reach that VITAL action level. This product is clearly not safe for milk allergic consumers. Mispackaging is a bad thing. Let's take a look at the mix are they making patties and. That serving sizes converted to milligrams how much carryover achieves it? A little over 8 pounds. If you have a 5000-pound mixer and a pound of material when cleaning it you will see a pound of the mix in there. In this particular case which is the greater risk? A little cross contact or mispackaging? Mispackaging is a greater risk. The hazard milk allergen is the same. Risk is exposure.

What do we have to do? We have to address the greater risk which is labeling and packaging controls. Some of the things we did was Institute line clearance when changing from not allergen to allergens. At a verification step to assure the packaging has been appropriately changed. This also means a has to be documented under FSMA. Then we installed a skinning system. Barcode standards are relatively inexpensive. If we had a barcode standard it would've gotten came back and the product would have never left the door. What can we do with that? That is some of the things we can do in the plant.

There are also other packaging things that happened early in the supply chain and material receiving. I'm not going to go to them in great detail but I'm going to summarize. At the printer,

can't ignore this as it is an area I am very interested in now. What happens at the printer. We already splintered no mixing, going to print something and put it on the label but when you order stuff we set it up to your product and we want to print all of the labels in one run. That is an area we need to work on. It has nothing to do with our protection facility if the printer. Having printing background since I work for magazines also know that you can use the wrong plate. Is usually wrong by plate you will get a incorrect ingredient statement that is on a package that looks like the right product. At the facility before production we talked about some of the things to do when you receive the materials. Look at the packaging read it and makes of the allergen information is there. Which also means the person on the dog has to have access to the system that tells you the allergen is there. More communication has to happen. There is a lot of information that the warehouse in person has to have that they do not have years ago.

One way to make it simple is to give them transparency that has the ingredient declaration on it from the package design. They can overlay that onto the packing material that readily tells them it does not look right and is not complete. My company tends to use the contain statement at the end of the ingredient declaration. It is more convenient for consumers. Other things to do at the facility during production. We bring out replenished materials cross took them. Use the barcode scanners. You can inventory how much he send out. If you send out packaging to cover 5000 cases a product and you send back packaging for 2000 cases but made 5000 cases, there is a inventory disconnect that should trigger you to investigate. There are things that we can do during production. Have barcode standards to look at the UPC code and [inaudible] systems that have a 2-D matrix. Tells them that the ? don't already have the right package but that they have the right version pulling the wrong version of a package can lead you to a recall situation. If it's the right package fine but it's not the right version because allergen profiles change. Generally, we like to take them out but sometimes you add them. Because of a new flavor.

So what we want to do is take thresholds and not stop managing allergens. We want to do a smaller method of managing allergens at all levels, so we can have these things covered to protect the consumers and it also protects our interest. I believe I have some resources here. I did not present a lot of data with references, but this is where my education comes from. I have been doing this since 1993. I have gotten a lot of cumulative knowledge over the years and this is some of the things we have used for this presentation. That is all. Thank you for your attention.

Roundtable Discussion

Moderator: Stephen Taylor, University of Nebraska, Lincoln, NE

All Speakers

Taylor: We have reached our discussion session. I would like all of the speakers to come to the front of the room.

Delaney: To Joe, on slide number seven you showed patient number one responding to 10 mg and the next one to 500 and the numbers might be off. I assume it is the same allergen [inaudible - multiple speakers]

Baumert: When we look at individual data we do not have access to analysis. We are talking about IgE responses. There is not a good predictor to identify those individuals. I will turn it to our researchers who have been looking at that area.

Greenhawt: I thought that was a perfect answer. You can predict the likelihood from the amount of antibody relatively within a fixed range depending on how good you thought the base study was. The severity has not necessarily been easy to do. There are other modalities to recent technique's basic cell activation MS cell activation test that might have a little more of a bite in terms of being able to predict severity. Overall it is a very difficult thing and can change in different days based on other cofactors. Let's take a look those are two triggers that would increase relative to a five-year-old boy that sat calmly every day. Those extreme examples or you take a 30-year-old who went out and had a lot of alcohol and takes an incentive in the morning to stop the headache it may become more sensitive in that situation as well.

Luccioli: I would add that in addition to IgE levels we also mentioned work on component levels where if you have additional information it tells you about whether the high levels are due to, are really significant or not. It may be because you are sensitized to pollen related protein or so forth that tends to make you tend to have a less severe our reaction. There is also pollen related food allergies. If you look at prevalence there is a high prevalence of allergies to fruits in the population. But we are not really talking about fruit allergies as major allergy hazards because most of the reactions are localized to the mouth area because people are developing allergies because of cross-reactive allergies to pollen. They have pollen antibodies that recognize a plant or fruit related protein and when it hits their mouth it causes an immediate reaction. So if, we are starting to get a little more information on other molecules people are sensitized to and it may help predict severity but at this point, basing it on IgE levels, it has not been shown to correlate with severity.

Taylor: There is a factor no one mentioned which is the other end of the cascade which is the cells release dozens of different mediators and different individuals are likely sensitive to these mediators. So, these are key mediators and histamine receptors in our body but may not all be legally reactive. Then we have dozens of other mediators less studied. That is probably why not everyone has the same symptoms. That can relate to severity as well. So, when you key steps [inaudible] you tend to have more serious reactions than someone who's key symptom is hives or vomiting. Because of the differences in their receptors other questions?

[Inaudible]

Audience Question: It becomes a challenge of knowing do you really have peanut in your product or if there is cross-reactivity because of the limitations of antibodies being sensitive enough and for the industry and limitation of being able to have an established method for detecting peanuts in a different matrix. I just wanted to raise that as an issue and the second question I had was in terms of cross-reactivity people can have if you are sensitive as Dr. Luccioli was saying. I was curious whether there was a threshold distribution curve for cross-reactivity for those patients. So that they are allergic to soy but then they have a mild reaction to peanuts, if that would be different.

Taylor: Maybe I'll take a shot at the first question. The cross-react to be in analysis is an important consideration. The method should be both sensitive and specific. So most of the commercialized methods on the market meet that criteria. They do not have must cross-reactivity or the cross-reactivity that they have should be well acknowledged in the product insert which, every user should read. For example, there is a peanut method on the market that is it acknowledged in the product insert to have some minor cross-reactivity it has been amazing to us that we receive several samples from industry users who hired a laboratory who neglected to read the product insert and told them they had peanuts. When in fact they did not. If you use the different method you didn't have the cross activity you would get a non-detect so you have

to make sure that the cross-reactivity is not significant at levels that would be of concern on a product recall basis.

Audience Question: Expect for peanut some of the antibodies are designed to give the region of peanuts is not necessarily the same ones used to detect allergens in humans are responding to them.

Taylor: Yes but, most of the peanut antibody used in the commercial tests they probably react to a variety of different allergens and in fact we have examine some kit's that primarily detect area three which is not surprising because that is something like 55% of the protein in the peanut kernel so you injected into a rabbit and he will see that he is that he is getting a lot and making antibodies to that. You will use those in your [inaudible] if I find areas three and a product that has been a and the label I'm going to assume safely assume that all the other peanut proteins are there. Clinically it is a much more significant peanut allergy but only present in six or 7% of the peanut kernel. Maybe I could use it as a marker, but we have to be careful because there is different stability and solubility characteristics. What I'm not going to worry about the fact that one antibody detects one epitope or and another detects a different one. Because even among peanut allergic humans with IgE antibodies they do not all detect the same epitope. So, we would be miles behind in analytically if we insisted on analyzing for clinically significant episodes in the first place. Someone suggested to me back in the early 1990s that that was what we needed to do but I said that will take the next 30 years if I get it done. Then the second question is a Joe question.

Baumert: Expect we can talk to clinicians about clinical cross-reactivity from the standpoint of looking at threshold distributions between populations peanut allergic and 5% that may be cross-reactive with PP or to my knowledge I am not aware of any challenge that has looked at the differential so we do not have that data but perhaps you guys know of data or clinical experience in that regard.

Greenhawt: I think what has happened is the detection methods have been so sensitive and have gotten only more sensitive. The antibodies themselves are relatively poorly designed. Things that are hidden. A peanut allergic individual may pick up so few to almost zero people to clinically react you will get a positive test and be at any amplitude, but I do not think the dose distribution would change. It which will be the person sensitized without clinical evidence or are they allergic which is 95% of referrals. My job is to sort out what you really allergic to. Sometimes all you can do is feed them the foods to see what happens. Risky but not hard to do. The distribution would not change the ED five would still be the same because they would have to be allergic.

Taylor: We did investigate an episode with the company. A company had high protein beverages on the market that was very high in soy and milk protein. Surprisingly for peanut allergic individuals or more reacted to the product severely. We managed to get samples from these individuals and at first the company thought it was peanut contamination, but we did not find any. It turned out that all of these consumers had extremely high IgE levels to peanut well over 100. So, they were in the minority in terms of their IgE levels. But they were all positive to soybean even though none of them avoided soybean. So, this product probably had enough soybean in it that it showed them for the first time in their lives that they were actually allergic to soybean. Prediction is set the four people down and do threshold challenges. They reacted to really small doses of peanut but would be higher if you set them down with the soybean one. If I was a clinician I may be scared to do the peanut one and would certainly start with the low dose.

I have a couple of questions from the viewers on the web. I think this question is primarily for Matt. What types of proteins are included in the oral immunotherapy or immunotherapy products? Specifically peanut proteins.

Greenhawt: That is proprietary so I actually do not know the exact mixture but if you go to the website they may have a description of that. That is all I would be able to say. The same thing for immune simulation. They are both proprietary and heavily guarded secrets as much as the 11 herbs and spices.

Taylor: Are all the proteins represented? Do you know if all the major allergens are represented?

Greenhawt: That's part of their trade secret, the degree to which they may be represented.

Taylor: I think these therapies have not been approved by FDA. I would be surprised if those responsible regulatory officials do not ask that question.

Greenhawt: I would. I don't know if they will get the answer, but the better question is what is responsible for making an immunologic change and that is not well-established. Let's say you were getting immunotherapy you know you need to have a certain microgram per milliliter the major cat allergen to promote what we would call change. So, there is a mix, but I am not sure if there is any data that shows you need to have X amount in that protein mixture to induce a change. I would say there are plenty of people getting immunotherapy from using flower that have been doing it in a private setting that have had successes without any characterization whether or not the characterization enhances the experience is something that remains to be proven but it does offer options.

Taylor: One of the other comments is that when we consume peanut or milk we often consume it as a heated or otherwise processed product. So, these materials used in immunotherapy include processing of the materials that are being used.

Greenhawt: Well with peanut you start with egg which is now allergen and the more you heat it you break up these bonds. Replaced IgE binds is held together and if you undo those you are looking at nonsequential epitopes. It is the confirmation fold. Egg and milk are highly exploitable when you eat them at higher temperatures for longer periods of time. Two out of 10 for each allergen will still react. With the immunotherapy would be in the base form not be extensively heated form. When you heat peanut you make it worse. You bring out stress proteins. These are all stress proteins and things that exist in nature that only get worse the more you heat it. All the peanut flour is defatted. The way in the concentration is right but there are processed to some degree. There are other forms of peanut or immunotherapy. There is a researcher in Australia and London that have been looking at boiled peanuts. The less high roasted the peanut is it is a more tolerable form. But these commercial products are going to be your standard peanut mix's and the milk will be, if you go on to clinicaltrials.gov you can see some registry for baked milk, baked egg, or immunotherapy standalone trials. Just a different concept but a variation on the same theme.

Taylor: Another question from the web. In your examples that you explained this fellow questions that you make an assumption in your mathematical case studies. You are assuming that the residual allergens are fully soluble and well mixed and well represented throughout the

lot. How might you address that type of concern as you try to figure out whether the dose the consumer gets might exceed the consumer's individual threshold and therefore be a risk?

Hegenbart: I do not think that it matters how much is left or how thoroughly the batch is mixed. In the end we're still clearing out the mixer and removing all visible traces of the allergen. No matter high how the concentration the amount should not be an issue at that point. I am assuming that we are going to eventually clean the equipment.

Taylor: If you do not clean it out it will end up in the next product and some unknowing consumer will be exposed.

Hegenbart: That is why I state that using thresholds is not going to change how we manage the allergens. But it does tell us a little bit about how much segregation is enough.

Taylor: More questions from the audience?

Audience Question: I have three questions. How widespread would you say the model is that you are presenting? That people are taking into account the VITAL action levels and calculating how much materials are left and using that to judge a batch of product?

Hegenbart: I'm going to give your question two answers. Do other people in the industry use VITAL to assess the risk in their processes? Yes. Do they use my exact model where they are looking at the backend to see a much carry over is necessary to create a risk? To my knowledge it is not widespread.

Taylor: I would agree he is the only one we know.

Audience Question: My other two questions are more clinical. They are different. With the studies, or desensitization studies I saw slides. In the interest of time no one commented on whether studies are proceeding in that area. Someone also mentioned gastrointestinal distress being a reason to drop out of studies. Any evidence that people with undiagnosed allergies are picky eaters and experiencing mild distress as a result of undiagnosed allergies? And if I think that is the case for my child how do I address that?

Greenhawt: Fish is very distal in the pipeline of products. Fish is something that has been looked at in Iceland and some of the Scandinavian countries as a protective factor. There is a study done in Iceland where they gave fish oil and it showed some protective effects of the development of allergies. That is with the omega-3 fatty acids. That is another cofactor beyond just something like peanut earlier. There is a large meta-analysis in PLOS. One a group from Imperial College that talks about some of the risk reductions. In terms of fish, fish are not all equal. The proteins is relatively conserved but we do have kids that will react to codfish but not salmon or tuna or they will react to tilapia. A lot like tree nuts. Which is why quality of life with those two allergens can be worse because it is not a singular like a peanut. Isolated G.I. symptoms without direct knowledge that you have ingested an allergen are nonspecific in terms of kids. It is a broad differential of what can cause a stomachache, vomiting, or nausea. Kids that are picky eaters that have recurring gastrointestinal pain may have symptoms indicative of [inaudible] which is a swallowing disorder. That can also overlap with a host of other things. Those individuals should be evaluated by gastroenterologist. I have rarely seen just G.I. issues. If you look at any textbook the differential for what can cause a stomachache is a dense page.

Audience Question: A number of speakers compared death from allergic reaction to lightning strike. You showed a dramatic side with a small sliver of allergen related recalls caused by cross contact. Is that a sign that we're worried about the wrong things or is that a sign that we have been successful in worrying about certain things?

Hegenbart: I am all over the map when I think about that. I think about that very thing. On the one hand with most large food manufacturers I think it is because they have been successful with managing cross contact. You will also find with many recalls a vast majority of them do not have illnesses reported until after the recall. That supports that the industry is doing a good job with cross contact control. I do also think that it is a matter of where the attention goes. This is me but I think the cleaning and sanitation part is an ultimate thing and everyone has devoted a lot of effort to cleaning and testing and let's test more and I think it is time to take a look at other parts of what make up a safety net of allergen practice and give them more attention. I am both ways on that. I think we do well with cross contact and those companies that do it and as I said in my presentation there are companies that have not gotten where they needed to be, but I do think it is something you can test for and write down a test result. It is not as scientifically sexy to make sure you have the right label. I think it is assumed to be easy when in the day-to-day operations it is not as easy as you think.

Baumert: I would also comment that we focus on one segment where allergen cross contact can occur in prepackaged foods. When you take about severe allergic reactions and fatalities there are additional segments that can contribute such as food service and catering. I think we have to put that fatality number in context to what we know and do not know. Again, I think there are other segments contributing to that.

Greenhawt: Also, don't underestimate the intense efforts of almost 30 years of preparing patients to treat symptoms. Most fatalities happen and if you get a bias sample that gets reported back usually there is a compounded risk taken. You see someone who has eaten something they should not have and very often they do not have their medicines with them. The number of cases I have seen looking back generally if you make a good effort, if it is a true accident and you treat appropriately very few kids failed to respond to treatment. We do not have statistics on how many kids failed to respond if you give epinephrine appropriately. We know 12% will need a second dose but that is after they have come into the emergency department. We do not know how quickly they received it but when we give treatment very few children fail to respond to that first dose. I would not change anything we are doing the focus because if you change that you have added another variable that could, if you relax certain things then maybe you will see an increase in fatalities. And may not be a noticeable thing. The lightning strike is in an unselected population. Not that it will be noticeably higher in an at-risk population. It can happen. The important thing to emphasize is that is 100% preventable.

Luccioli: I will also reiterate that I think we have these numbers that are in the literature and public health agencies adopt them because it is what clinicians were reporting. They turned out to be based on data from a few counties in the United States. Then you extrapolate. Maybe there was never that high amount to begin with and maybe there has not been a drop in the number of fatalities, but I do agree with everything that has been said. I think there have been measures from the industry level, public health, and treatment with epinephrine and other drugs that are probably keeping those numbers low.

Taylor: I think in terms of having an impact on recall data it would be really helpful to industry if they can learn more from the recall data that FDA and USDA and FSI is half. It would be nice to know how many of these recalls were associated with consumer complaints. That is almost

impossible to figure out. In some cases, it is there. Maybe it is impossible for the FDA to know this, but I wonder if all of the recalls are associated with potentially hazardous doses.

Luccioli: We did look at that specific question about recalls triggered by or associated with consumer reactions from 2005 to 2010. We found that milk was definitely the most common associated allergen with these adverse reactions. The numbers were probably, it is hard to tell if we are getting all the information as well because sometimes they may reported to industry and not tell us. It was probably 5% of recalls associated with consumer

[captioning pauses for an extended interval]

Taylor: We did a study with the group at Mount Sinai. We did not find a lot of detectable allergens using products with or without precautionary labels. So, the data seem to be different for the US versus the EU. Maybe, it is hard to make those comparisons because the amount of food manufactured in the world versus the amount tested is a big difference.

Luccioli: I just want to make a comment on that. That we do not know if this was due to the reactions if people are coming to the US like if a child has a reaction at school. It is also a requirement that they go to the emergency room. Even if they had a relatively mild reaction who knows the severity of the reaction but there are protocols. I know it is a good point. And you are right in this case they were admitted so maybe there was but sometimes using that data, I've been looking at some data but I cannot say for sure. But there has been an increase if you look at data with people coming to the emergency room for food allergic reactions. It has increased over the last decade. I think consistently showing that. Now is that because there are more severe reactions or are people just going to the ER more because they are told to go?

Greenhawt: With disclosure I also had a paper accepted looking at the cost-effectiveness of sending a child who responds to epinephrine, what is the cost effectiveness of sending them to the emergency room? It costs just under \$1 billion to prevent one's death and over \$1 billion to save one life. It shows that if you look at the action plans they are telling you it is completely backwards. If you even have suspected or if you believe the child is sensitive inject with epinephrine before the symptoms developed. There should be limited circumstances where that would actually make sense. Especially because the drug has a half-life of 15 minutes and digestion is unpredictable. Some people can react within two hours so you, so you could end up burning a dose. We are driving kids to the emergency room and driving them to call 911 and do things that often have little value based on the resources we have. Other choices would provide better value. Whether or not that is inflating or conflating statistics that show more people are showing up with a chief complaint when you look at that data it is the complaint of and then it's the emergency physician diagnosis of which may conflict with what an allergist would diagnose [inaudible]. Yes, there is more prevalence and incidents of this, but I do not think as many kids are going as that statistic would say and we may be sending more kids who are stable to receive care that they did not need at that point. What are you going to tell a parent? Do you tell a parent who is scared and does not know and just wants their child to be safe? You going to say do what you are comfortable with but when you analyze this some of the decisions we make probably do not have much value.

Taylor: People are patiently waiting to ask questions.

Audience Question: Since this is a worldwide issue can you expand on how other countries handle allergy risk assessment management and whether some have been more successful or promising?

Baumert: I would say that Japan has been the leader in that regard. Back in 2002 they put in their regulatory limit of 10 ppm protein from the allogenic source. It seems to be rather effective although they have not really collected data to evaluate the effectiveness. When we talk to some of our clinical colleagues in Japan they have not seen an increase in the number of reported allergic reactions in the community as well as reports back, of clinics. It seems to be effective. Switzerland, I'm not sure where that is derived from, but I do not think any food company follows the thousand parts per million limit as a regulatory limit for allergens. So, I would disregard that as a regulatory limit for allergen action levels. Beyond that there has been additional evaluation of the threshold population distributions. The VITAL reference doses and so forth. Various individual working groups in primarily Europe have looked at that as well as the VITAL group in Australia. Some of the regulatory agencies are now taking some interest in that. And unofficially they are looking at trying to derive a reference value. None of them have been put in place at the moment. There are proposals and some will perhaps be referenced on the VITAL reference dose Belgium propose using ED five value part based on the PATS study and based on the mild reactions involved. I think there is a diversity of different things going on. What I would like to see is a harmonized approach. I think it will become quite difficult when trying to manage from a company standpoint that this country has a reference value of .1 and this one has a reference value of 1.5. That makes it challenging in that regard to use that as a benchmark. So again, I think there needs to be additional efforts and global harmonization as we go forward.

Greenhawt: I would add that we have an obligation and those who want to figure it out what the threshold might be because if you can prove, one thing he did not emphasize enough with how much the quality of life improved in the patients who were told all of a sudden you have 15 or 20 prepackaged products that you are simply avoiding because they may or might contain a hypothetical sub gain. There is great debate in the field with the advocacy groups publishing a study years ago that more or less suggested that parents weren't interested. That maybe one sample of the population. I know from speaking at other things and talking to industry people that I think there's more consumer curiosity as to what someone may be able to tolerate. And needs to be handled responsibly. We also show the sister publication that if you can bring someone into your office and do this one-shot type of challenge, that is a cost-effective policy compared to having someone avoid this for 15 or 20 years with all the recurring costs is. This is under \$50,000 of quality adjusted per life year. That is well under their standard so there is value to doing this not only economically but to quality of life as well.

Audience Question: Thank you for a formative session this morning. My question is related more to when coming up with referenced doses in determining ED numbers etc., elements that affect the quality of the test material in terms of the percent purity or distribution of the important component, is that a component of concern in the data analysis? And if it is, is there a way to address those elements when looking at those distributions? Is it potentially having an impact on the final numbers?

Taylor: I think one of the key points is that the data is normalized on protein levels from the source. So, if you look at milk data most of the challenge studies have been done in humans and have used nonfat dry milk which is a fairly standardized material. 35% protein give or take, or it is used in infant formula. Then you have to know which infant formula what the percent protein was in order to use that data. But it does assume that the milk proteins are there in equivalent distributions and we know the variability from cow to cow and breed to breed and farm to farm. I am not sure that is a big uncertainty factor in the overall data compared to a lot of the other things we have.

Baumert: I think Steve covered it well. On many of these challenges are clinicians going out finding the food masking it in another matrix. Most of these are again, food products. What we have done is evaluated the type of food product and get a normalized sense of the protein value. Sometimes that was reported by clinicians at other times we have to rely on standard databases or protein content. With that I would say the model averaging approach helps bring in uncertainty of different types of foods in different studies and so forth. So, we're trying to bring all of that variability into the analysis as well. So, would we see a significant difference if normalized protein values between light roasted peanut flour versus medium roast peanut flour in a challenge? I do not know that we can say that with 100% certainty, but I would say it is probably not a significant amount of variability in the overall analysis.

Greenhawt: Kids want either candy or peanut butter from having done hundreds of challenges. Remember feeding your own child what they will like any and now you are dealing with a picky child who has been told it was poison and they want nothing to do with it. I think we are stuck a little bit with that as a potential constraint. In looking at the threshold as a researcher and clinician I never once worried about that of all things.

Baumert: Your question may go towards how we are proceeding with the immunotherapy type challenge materials. That is a whole another conversation that I do not think we have time to get into.

Taylor: I don't think we should get into it right now because we do not know enough to comment. Scott the one person has the same question that I asked you before about you didn't really mention particulate contamination in your presentation. I am paraphrasing these questions not sure I'm doing the best job. They are long questions.

Hegenbart: Particulates are the bane of my existence. Dealing with a product where you have distribution yes that is much easier to deal with and calculate. When it comes to a particulate that usually engages a different degree of scrutiny. I often times have much more conservative when dealing with particulates. Unfortunately, in my case I do not deal with particulates a lot except in cases where it is pretty obvious and extreme. Particulates are not part of the model I used. I used things that were comminuted products or something more easily to be consistent. Particulates bring another dimension to it. I am still thinking about that trying to figure out a way to make myself happier with particulates but that presents a challenge.

Taylor: One of the comments we would have is open invitation to the food industry. Let us help you measure the weight of your particles. So, we can use quantitative risk assessment to evaluate the risk of one particle part two particles, three particles and that would help put that into better context. I think the occasional presence of an unintended particle is a major driver for precautionary labeling in industry. Because there are lots of cases where you have a hard time figuring out that there is not a single crumb left anywhere.

Baumert: I do not have additional things to add. Steve hit the points I want to cover. When you think about a particulate it is a discrete dose. So you can think about particle size and so forth and think about what dose should be delivered. That's why thinking about size and distribution with the particulates through the production cycle can be modeled in different quantitative methods.

Taylor: We did that once with sesame seeds. Didn't you? Because sesame seeds, that is the particle that would usually be left. So how dangerous is it? With a sesame allergic person

typically react to a single sesame seed? The answer would be not very many. That assumes that they solubilize all the protein as it goes through the G.I. tract. I think that is another major known with sesame seed.

Hegenbart: I'm going to chime in on the discussion of particulates. We talked about limitations of testing. If you have a particulate it is easy to get the allergen in something and not in something else. That is why visual inspection is still a good foundational tool to assure that you have cleaned your equipment.

Taylor: The speakers were told this morning that we should not get into policy related issues but of course here's a question that specifically policy related. Whether FDA is considered adding additional allergens to the list back Congress established when they passed the Food Allergen Labeling and Consumer Protection Act. The FDA did not get to decide on its own. Maybe I will change this question around.

Luccioli: Certainly, we are all looking at, we are aware of these allergens. Many of you know there is a citizen petition of sesame. Signed by many individuals and clinicians. We are certainly looking at that, but we also realize that the law does not really, what I think is misunderstood is that they think FDA develop [inaudible] but it was developed by Congress. We implement [inaudible] but it does not really have a specific statement on modifying the allergen list or adding new or modifying those allergens. So that is a challenge. It is not a straightforward process if we want to consider adding another food allergen. We probably need to start looking at, but you know we do not have criteria is to establish if we wanted to establish a new food allergen. Canada develop criteria recently and ended up adding mustard to their list of allergens. While excluding garlic and onion so I think that is a fair thing [captioning gap].

Taylor: What the Canadians did was establish a process but ignored it when it got to mustard. Because it did not fit their criteria. But, they decided in their regulatory discretion to add mustard because it is often hidden under spices or other collective terms, flavor. When the National Academy of Sciences group looked at this back in 2016, we commented that the list that exists in many countries in the world were not established completely on the basis of the scientific and clinical facts. It is really hard to justify on the basis of science or clinical data, why Europe has celery and mustard and why Taiwan has mango and why Korea has tomato. They just do. It would be nice if it was based on clinical and scientific fact. Then maybe we could have global harmonization although you do need to consider cultural differences. I think if Americans started eating buckwheat like the Japanese do we would probably have buckwheat as a commonly allergenic food. So, there is that consideration.

Brian is signaling that the section has come to an end and I would like to thank speakers for the wonderful presentations and the audience for good questions. Thank you.

Delaney: Once again, on behalf of everyone here thank you for taking the time to prepare wonderful presentations. I would like to remind everyone in the room and on the phone we have more planned for this year and next. Coming up bioprinting for testing, food flavor modifiers and early next year, is the time passed for cancer/noncancer risk assessment. To remind everyone these materials will be available on the website no charge at www.toxicology.org. Thank you all for your participation. If you registered to attend you will receive an email with the survey link. Please fill it out and it will be helpful in future planning. With that thank you all for attending and thank you to the speakers for coming.