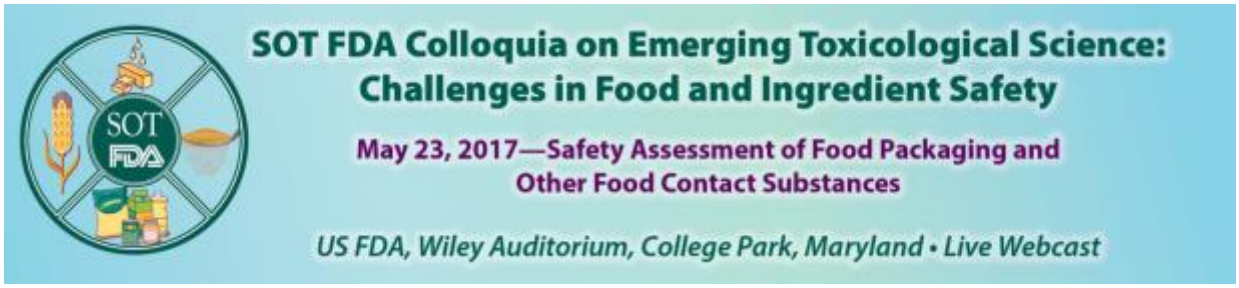

Real Time Captioning

Chair: Charles Barton, PhD, DABT, Valspar Corporation, Sewickley, PA
Co-chair: Jason Aungst, PhD, US FDA, College Park, MD

8:30 AM-8:45 AM	Welcome from FDA Michael Adams, US FDA, College Park, MD
	Welcome from SOT Peter L. Goering, SOT Past President, US FDA, Silver Spring, MD
	Speaker Introductions Charles Barton, Valspar Corporation, Sewickley, PA
8:45 AM-9:15 AM	Overview of Regulatory Science of Food Contact Substances Michael Adams, US FDA, College Park, MD
9:15 AM-9:50 AM	Overview of Key Food Packaging Steve Hentges, American Chemistry Council, Washington, DC
9:50 AM-10:30 AM	Can Coatings, Primer, and Safety Assessment: Communicating Evidence of Absence Mark Maier, Sheperian Toxicology, Albuquerque, NM
10:30 AM-10:45 AM	Break
10:45 AM-11:25 AM	Migration and Exposure Considerations Jessica Cooper, US FDA, College Park, MD
11:25 AM-12:05 PM	Packaging Innovations to Improve Food Safety Maria Rubino, Michigan State University, East Lansing, MI
12:05 PM-1:00 PM	Roundtable Discussion Charles Barton, Valspar Corporation, Moderator All speakers, plus Gina Solomon, California EPA, Sacramento, CA Mark Feeley, Health Canada, Ottawa, Canada

The text below is the captioning of the live colloquium, not an official transcript.

8:30 AM-8:45 AM Welcome from FDA--Michael Adams, US FDA, College Park, MD

Good morning, everybody. I would like to welcome you to the 12th of the series in Society of Toxicology and FDA colloquia on emerging toxicological science. *Challenges In Food and Ingredients Safet, Safety Assessment of Food Packaging and Other Food Contact Substances.* My name is Michael Adams, Deputy Director of the Office of Food Additive, Safety. On behalf of the Society of Toxicology (SOT and U.S. Food and Drug Administration (USFDA), I would like to welcome everyone in the room and the folks listening and watching online this colloquia. The USFDA is partnering with the) to provide a series of four half-day training sessions based on a memorandum of understanding recognizing our organization shared interest and scientific progress and disciplines that directly and indirectly affect human and animal health and medicine. This MOU signed a few years ago outlines the opportunity for collaboration between our organizations in producing training events, workshops and conferences to continue to engage the newest toxicology relevant to the FDA's work. These colloquia are intended to provide a forum to engage in the newest toxicology methodologies and inform the work at FDA Center for food safety and applied nutrition employees by utilizing leading experts in toxicology from around the world. In addition the colloquia are open to the public and offer the public an opportunity to hear some of the same information used in our regulatory decisions. I will point out the colloquia are not intended to offer a public forum to discuss or make recommendations to the agency on regulatory issues, but rather intended to discuss toxicological and regulatory science. As I mentioned, this is the 12 in the series that have been held over the last three years. Our focus is going to be on food packaging and food contact substances and in their safety assessment. It is being chaired by Dr. Charles Martin of the Valspar Corporation.

In addition to myself, today's participants include Steve Hentges from the American Chemistry Council, Mark Maierr from Sheperian Toxicology, Jessica Cooper from the Office of Food Additive, Safety at the U.S. FDA and Maria Rubino is from Michigan State University. After the formal lectures we will have a roundtable discussion that will be chaired by Dr. Martin and our speakers from today. Just a note at the end of each speaker's presentation, we will take clarifying questions. Please save other questions for the panel discussion. For those of you online you can send your questions in via the chat function on the WebEx. Feel free to send them in at any time, and we will get to as many questions as we can within the allotted time limits.

Finally, a few administrative items:
Restrooms located just outside the entrance on the top floor and at the bottom entrance. As you leave they will be on the right-hand side of the corridor. We will have microphones in the audience. There is one on either side for people in the room to use when you are addressing your questions. So everybody online can hear, if you want to ask a question the sure to use the microphone. Finally, I will put out a plug for lunch. FDA employees and staff fellows and anybody here and interested can have lunch with the speakers immediately after this colloquia.

It is now my pleasure to introduce Dr. Peter Goering, SOT Past President to whom I will turn the microphone over.

Welcome from SOT--Peter L. Goering, SOT Past President, US FDA, Silver Spring, MD

Good morning, everyone. Welcome to today's colloquium. It is a pleasure to introduce the colloquium on behalf of the Society of Toxicology, the society is extremely pleased to be a partner in this collaborative activity that has been ongoing for two and a half years and has been widely successful beyond our expectations when we started.

This is indeed a partnership and we're very grateful to Alan Redman from CFSAN who helped spearhead this from the CFSAN side and Dennis Keene who is a strong supporter of this activity. We should all be thankful for their interest and continued interest in this activity.

I think the collaboration is successful because of the complementary missions of each of our organizations. The USFDA has an overarching mission to protect and promote the health of the public, and the society has a mission to create a healthier and safer world by advancing the science and the impact of the discipline of toxicology. One of the key areas each organization promotes is the training and support of our staff including our toxicologists. This forum we have here in the CFSAN provides a great deal of impact in this area to develop our toxicologists.

We have held 11 previous colloquia on various topics in risk assessment and food safety and today is our 12th. This has all occurred in the last two and a half years so the organizing committee and the collaboration have made a strong effort to provide these colloquia to staff inside FDA and outside FDA.

One of the major successes is the accessibility of these colloquia around the world. This map illustrates the 24 countries where individual scientists have been able to participate through our WebEx capability. In the last three or four of these colloquia, this is a pattern. While one can participate in listen today, all of these colloquia are available on the SOT website at toxicology .org and one can listen at your own pace at any time and there is no subscription fee.

Again I am very pleased the collaboration between SOT and FDA will continue that has been implemented by renewing the Memorandum of Understanding to continue the sharing of our expertise and resources. Last spring, the SOT President, John Morris, and FDA Chief Scientists held a re-signing ceremony at FDA. Other representatives from FDA and SOT present.

These events don't happen in a vacuum and I would like to take the opportunity to thank some key players that have led to the success. One being, Ivan Rusyn led the organizing committee since its inception. He stepped down on may first and we owe him a debt of thanks for his strong efforts to lead this group to provide state-of-the-art presentations by many experts in the field. I am pleased to announce that Brian Delaney from DuPont Pioneer in Iowa is going to step in and will chair the committee. We expect the committee to continue to be a strong success under his leadership.

I would also like to thank the SOT Headquarters staffer does the behind-the-scenes work to make this successful with registrations and taking care of our speakers. To thank Betty Eidemiller and her staff at SOT Headquarters. Thank you also to the guys up in the booth and making our WebEx successful around the world.

This is our organizing committee as a stands now. Brian Delaney is the new chair. We have new people from FDA and also from the Society of Toxicology at large, which meet frequently

to plan and organize these colloquia. If you have ideas for topics for these colloquia, please contact one of these committee members and they would be happy to bring your idea forward.

Let's get started with today's event. I would like to introduce Jason Aungst from the Center for Food Safety and applied nutrition. He is one of today's co-organizers and I would like to call him to the front.

Co-chair: Jason Aungst, PhD, US FDA, College Park, MD
Introduction of Charles Barton

Thank you, Peter. I also would like to thank the organizing committee for putting this colloquium together. I'm looking forward to some interesting discussion on food contact materials. For those participating in the webcast if you have any questions for the speakers or for the panel session, please send them to me to the online chat and I will be keeping track of those. I have the pleasure of introducing our chair Dr. Charles Barton. He is a global manager of toxicology and risk assessment for the Valspar Corporation and worked in a number of important roles notably as the state toxicologist in Iowa and serves on the Board of Directors for the American Board of Toxicology. We are fortunate to have such an expert toxicologist. Who also had experience with food context materials. Welcome Dr. Barton.

Speaker Introductions--Charles Barton, Valspar Corporation, Sewickley, PA

Thank you, Jason. I'd like to go over the agenda with you. First we will go over an overview of regulatory science and food contact substances with Mike Adams. Then we will look at an overview of key food packaging material. Then we will look at can coatings, primer and safety assessment and communicating evidence of absence of toxicity. Finally we will look at migration and exposure considerations.

Packaging innovations to improve food safety and this will be followed by a roundtable discussion. All the speakers will be invited and we have two invited guests who will also be present. Dr. Gina Solomon with the California Environmental Protection Agency, and Dr. Mark Feely with Health Canada and they will go into how they use the best available science in reviewing food contact substances. At this time, I would like to invite Dr. Mike Adams to the stage. Dr. Adams received is a Bachelor in chemistry from St. Michael's College in Vermont and his MS and PhD in chemistry and pharmacology from Cornell University. He was a research foundation fellow for two years at Columbia University. At the end of that fellowship, he joined the faculty at the Chemical College in Center in Philadelphia. He studied chemistry of chemo reception. He then joined the U.S. FDA where he has worked for over 20 years. Currently is the Deputy Director of the Office of Food Additive, Safety in the Center for Food Safety and Applied Nutrition.

Overview of Regulatory Science of Food Contact Substances – Michael Adams, US FDA, College Park, MD

Thanks very much for that kind introduction. I'm happy to be here to speak to you today. I have to disclose in the interest of full disclosure I am not a toxicologist. I am a chemist, but I am grateful you let me in the door to talk. I'm going to primarily focus on the food contact notification process, how food contact materials moves from say conception in the laboratory through to authorization by the FDA and onto the market. A couple of facts about the FDA; the

agency is responsible for about $2 trillion in regulated medical products, foods, cosmetics, dietary supplements and tobacco. This amounts to about $0.20 of every dollar of annual spending by U. S. consumers. This is quite a big responsibility, and we cover a lot of ground in the American economy. The agency itself has about 16,000 full-time employees and our annual budget for 2017 was just under $5 billion.

A few words about the Office of Food Additive Safety, which is where I work and Dr. Cooper who will come later, we have also worked in the same office. We are responsible for the safety of food ingredients, food packaging, food processing equipment, and this includes things like sources of radiation used to inspect foods from foods derived the products of bioengineering. Our products and office output is food additive petitions, food contact notifications, color additive petitions, GRAS notices, generally recognized as safe ingredients and a few other products that come before us for safety decisions.

As I said, we are responsible for food additives. These enter the marketplace after a review and approval of food additive petitions. These are typically done for direct additives and things added directly to food to influence the properties of food although they can be used in certain locations for in direct additives, things not intended to get into food directly but do such as through packaging materials, and I will explain the conditions where we might use of food additive petition for food contact materially to run. We also have color additive petitions. These are chemicals designed to impart color to food.

Too the notification program we handle food contact substances, food contact materials, and these are things that contact food. This is generally not intended to have any effect on the food. We also handled through handle through a notification program generally recognized as safe ingredients and then we have programs for biotechnology and other minor products. We have 138 full-time employees in our office and our budget is just over $6 million this year which is quite a small piece of the overall FDA budget but we have a fairly large responsibility in the actions we take.

This talk will present a brief overview of the approval process for food contact substances. I would like to discuss about roles and responsibilities in the process and overview the safety standards under, which we operate. Then I will go over a little bit about the concept of harm as it is defined in the law because it is a little different than what people think of when they think of the concept of harm. Most of what I say is going to be on the administrative topics later on. Dr. Cooper is going to go over chemistry and exposure parts of the process and the other speakers will comment on the toxicology issues that arise in the notification process.

What is a food contact substance? The FDA modernization Act of 1997 defined a food contact substance as you can see on the screen. We love and operate by definitions so it is specifically worded to cover what we are intending to do. Any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting or holding food if such use is not intended to have a technical effect in the food. The whole concept of this is things that are not intended to interact with the food in any particular way but there may be things in the packaging materials that do migrate into food as a consequence of their use and we want to make sure those migrating materials are safe before they enter the marketplace.

As an example of food contact substances, we’re talking about instant adhesives used in packaging materials to glue boxes together. Coatings for people or plastic or coatings for metal cans as well as paper and paperboard. Polymer materials used to wrap the package food and store food in containers and the monomers that form the polymers that may actually migrate

into the food as residual materials. Colorings used to turn polymers different colors like the blue food storage bins you can buy in the grocery store. Substances like antioxidants and production aides that had technical effect in the packaging material to make sure the packaging material is durable and does what it is supposed to do. It does a breakdown in the process of being used. We also regulate things like sanitizers used in food processing plants.

A little bit about the notification process itself. For the last 17 years the food contact notification process has been the primary means I which the FDA authorizes new uses of food additives that are food contact substances. This process was intended to replace to a great extent the previous food additive petition process for in direct additives. The food contact materials are a special class of in direct additives. We reserve the right to decide what process we will use to handle food contact materials. Typically the exposures to chemicals migrating from food contact materials were very low so the notification process is an ideal situation for regulating those. There are occasions when the migration might result in a higher than normal exposure. We would reserve the right to handle those exposures through a food additive petition process. The differences the food contact notification process, the notifications come to us as a complete data package and a declaration by the sponsor that they have made their safety determinations and considered all the chemistry and toxicology data available. In the opinion of the sponsor the material is safe. When we get a food contact notification, we have 120 days to review it. If we don't object to the notification the sponsor is free to market the product. If we find there are problems, we can invite the sponsor to withdraw the notification pending further consultation or we can't object to it if it comes to that.

For high exposure issues, we feel those are better handled through the food additive petition process. The food additive petition process, if the petition is perfect and can move as quickly as the notification, but generally the petitions have questions that need to be answered, questions on safety and sometimes chemistry or toxicology questions. The petition process is a more iterative process where we received the petition and we file and review it. If we find efficiencies, we go back to the petitioner and say these are the deficiencies in Kenya correct these. Then you can submit your new data and we will consider it again. This question and answer iteration can take a longer period of time, but generally we use it when there are significant questions that need to be answered. I would say 99% of the food contact materials are handled through the notification process. If the notification is good, 120 days, it is good to market. Another advantage of the notification process is the notification is exclusive. Anybody that submits a notification the permission-to-market only applies to the sponsor and not anyone else to anyone else who might have a similar or identical material. This is different than the food additive petition process, which results in a generic food additive regulation listed in the code of federal regulations. Anybody is free to use food additives listed in the code of regulations as long as they adhere to whatever specifications might be contained in the rules. There is a little bit of the difference in the way things are handled and a little bit of a difference in the outcome of the two processes.

When should the FCN be submitted? FCNs are acquired for new food contact substance, as well as, for a new use of an existing food contact substance. This is the exclusivity principle, I just mentioned. They are required for a new manufacturing process. They may be required when a sponsor changes a manufacturing process. And if a new supplier wants to marketing material they have to submit a new food contact notification. One of the planes points I will make about changing manufacturing processes is we offer the opportunity to review the process before the food contact notification needs to be submitted. If we decide to change in manufacturing processes so minor as to not result in a change in purity profile on a food contact substance, we may say no new notification is necessary. We would just enter the

change into the record and the company is free to proceed. If the manufacturing process has changed significantly, there will be a requirement for a new food contact notification because the nature of the additive itself may change. Not the additive at the purity profile. Before submitting the FCN or any kind of a change, we encourage folks to go through our premarket notification consultation process. This is a free service offered to anyone. We would like to discuss what we're going to submit and we can do a quick review to make sure the data package you're thinking of giving us is going to be complete as we can get it before we do a formal review. It also helps to prevent people from doing unnecessary chemistry or toxicology. Sometimes these experiments can be very expensive and we don't want to have people start down a path that is not going to result in any information we can use in our regulatory process. We have seen companies in good faith would do a 2-year toxicology study only to come in and find out it is not something we can use board was improperly done. It is always good to consult with us before starting to do anything. We found that results in a much happier clientele in the end. It also makes it easier on us when we get the data packages because if we say we want you to do something, we want you to do it but if we tell you we don't way to do something, we are not going to go back in most cases and ask you to do something again.

In terms of roles and responsibilities, the notifier has the burden to demonstrate there is a reasonable certainty of no harm from the intended use of the ingredient. I will get into reasonable certainty in a few seconds but in terms of what the FDA is required to do, we are required to assess whether we have received and adequately documented dossier of information that will allow us to reach a safety decision in a reasonable amount of time.

What does this phrase reasonable certainty of no harm mean? It is a term of art used that goes back to the 1958 food, drug and cosmetic act which was the last time there was a reef brief formation of the food and drug safety laws. I will quote from the language in the original documentation for the law. The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty no harm will result from the proposed use of an additive. The writers went on to elaborate a little bit saying it does not and cannot require proof beyond any possible doubt no harm will result under any conceivable circumstances. They felt it was important to make that clear because there is a tendency for people to try to have absolute safety, the concept of absolute safety doesn't really exist. The best we can do is to enforce the concept of reasonable certainty of no harm and that is the principle under which we operate in the office of food additive safety. They also define harm, it is harmful if it affects health, not if it is simply an undesirable or -- our concept of harm to consumers safety and the other concepts of harm are left to of the regulatory agencies to deal with.

The food contact notification program in general, in the food contact notification we use the exact safety standards and basic data recommendations we have traditionally used in the food additive petition process. This consists of a collection of chemistry, toxicology and environmental impact information prepared according to our guidance documents and the regulations under which we operate. The safety standard is the same for all of our regulatory products in OFAS. These FCN is effective 120 days after a food contact notification is excepted unless the FDA objects. One of the things I want to point out, there's a bit of confusion about when a FCN is excepted. It is not the day it comes in to our mailroom, it is the day when we look at it and decide the package is complete and generally we will send out a letter saying it has been accepted for review and that starts the 120 day count down. If we conclude there is a reasonable certainty of no harm caused by the intended use, we will allow the FCN to become effective. Under the law no further notification is necessary to the manufacturer but as a courtesy we will send out a letter the stating the conditions under which

the FCN is effective and then we will give you the date it is effective and that is just to ensure there is no confusion about what the appropriate start date is.

In our initiative to be transparent to the public, we will publish on our CFSAN website an inventory of affecting food contact notification. Anyone from the public can review that and find out what notifications are in effect. If the notification is withdrawn before it becomes effective, that information is held in confidence and we don't release that information to the public. If we object to a notification that rejection and information on which is based is public information. Withdrawals requests are in our system to avoid having the objection disclosed. A lot of times the objections are things that can be corrected through fairly minor modifications to the notification. We try to catch the minor problems before they go into the review process, but there is no guarantee we will catch everything. The only thing we do guarantee is after 120 days you will get either a commission to market or an objection or a withdrawal request. In terms of the safety standards we use for a review, we pledge we will provide a fair evaluation of all the data submitted. We understand our decisions are made in the absence of complete knowledge. That is the premise under which the whole notification process operates. We make time-dependent decisions and our decisions have to stand scientific procedural and legal challenges from all sides. We try to do the best we can. We've got a very good track record with these materials and we pledge to our sponsors and the public we will maintain these high standards of review. The standard of safety is not a risk-benefit analysis. It is based on an analysis of the safety and this concept of reasonable certainty of no harm I mentioned previously. We use the same standard for all of our regulatory products at OFAS.

Just a couple of words, a lot of this will be talked about by Dr. Cooper later on this morning. In terms of a food contact notification, what are the elements that go into this? Some of the things that have to be described in appropriate detail I would say would be the identity of the material and believe it or not, we have had some notifications, and in the old days some food additive petitions for the provider didn't actually know what the material was. Sometimes it is understandable.

Polymeric materials can be very complicated structures, but you should be able to describe the identity of the material in some way that makes sense to our chemist. If you can't, you're not going to get very far with the notification or petition. We ask for identity information to include name and chemical abstract service number if it is available. A structure, molecular weight, is ago characteristics of the material. We wanted description of the manufacturing process in full. That would include conditions of time, temperature, catalysts, solvents and so forth. That information we can get a better idea of the impurity profile. If you have a specification Jude think are important those should be disclosed and they become part of the notification of illegal identity of the substance. Stability information, we would expect food contact materials and food additives are stable under conditions of use but we ask for information to demonstrate they don't break down under conditions of manufacturing processing and storage from the time they are manufactured to the time the consumer receives them in the grocery store. We also ask for a description of the technical effect and use conditions. We look for data to show the minimum quantity of a material is being used, this is particularly true for food contact substances that are stabilizers and things like that in polymers and packaging materials. In the past we have seen a few occasions where people try to load up a little bit on the additives. They will have a level that may be a little higher than necessary for the technical effect. If we keep that level low that reduces the exposure to the consumer. In analytical methodology that is used to describe the material ask for the method to be submitted for our review and an estimate of dietary intake, and Jessica will go over all of that in some detail.

The other components of the food contact notification include toxicology data. Probably what is most familiar to this audience. We ask for a full disclosure of the toxicology data and anything developed by the sponsor to support the safety of the additive plus a review of the literature relevant to the additive with the food contact material itself should be submitted in this comprehensive toxicology profile. This information is used in combination with exposure data to determine whether the use is safe. We also have an environmental review component. We are bound by the environmental regulations to do a review of the environmental impact of additives so we have some procedures that have to be followed for providing environmental data to make sure the impact is negligible, or if there is a high impact situation an environmental and environmental assessment needs to be done so we can see exactly what is going on.

If those requirements are met and the data are developed properly, in consultation with us, we can provide a quick pathway to market for food contact materials.

That's about all I have to say about the process. I don't know how many questions you want to take, but I have a couple of minutes to answer. I just wanted to point out one last slide on the references. We try to put out as much information as we can on our website. The design of the website is a little obscure, but if you persist in finding your way to the food packaging section, you can find our inventory of food contact materials and find our guidance documents. We have guidance documents for chemistry, data and toxicology data. We have information on how to do your environmental evaluation. This information I think is useful if you read it first before you start asking questions but when you read it, if you have questions we will be happy to elaborate or answer. We also have on various places on that series of web pages that revolve around OFAS activities, we had inventories of GRAS notices and food contact notifications and the other products we regulate. For food added tip petitions, that information is found in the CFR. There is a link and the top link is the electronic code of regulations and fairly easy to get to. You can search for the additives you are interested in. For the old-school folks like myself you can still get the CFR in print. I think that is it. Thanks very much. I would be happy to answer questions later. [Applause]

Thank you, very much Dr. Adams for a very informative presentation. Now I'd like to Dr. Hentges, Executive Director of the Polycarbonate Global Group of the American Chemistry Council. This group consists of leading manufacturers of BPA in polycarbonate plastic. It conducts a comprehensive program that includes human health and environmental or eco-talks research along with a wide range of communications and advocacy activities. Pair to joining ACC, Dr. Hentges spent 20 years with a chemical manufacturer working primarily in a series of assignments that focused on product safety, regulatory compliance and product development. He received his PhD in organic chemistry from Stanford University. Dr. Hentges.

Overview of Key Food Packaging – Steve Hentges, American Chemistry Council, Washington, DC

Thank you for that introduction. I have to start up with my conflict of interest statement. I am an employee of the American Chemistry Council which is a trade association or industry association based in Washington, DC. We represent a diverse set of companies involved in the business of chemistry. Like Mike Adams, I suppose I need to give you a disclaimer of sorts, I am also a chemist by training so I'm not a toxicologist although I have been known to pass as one from time-to-time. I think I passed fairly well from time-to-time, but I am a chemist by training.

My topic was to give an overview of key food packaging. I thought it would helpful to start with the definition of food packaging and what it is. I don't think FDA actually has a definition for food packaging so I went to Wikipedia to find out. This is what I found. Food packaging is packaging for food. That's a little bit circular I suppose, but on the other hand food packaging may be so intuitive and obvious it might be a challenge to define it in any meaningful way, at least for the short definition. To be fair Wikipedia does go on to talk about the functional attributes of food packaging in terms of protection of the contents in various ways so food packaging may be so obvious we don't need to define it much further. As Mike Adams mentioned, food packaging is regulated by FDA as a food contact substance. I don't need to go to this statutory language. You have seen it before and I expect everyone has this memorized.

At the top level, what is food packaging made from? There are number of material is used in a variety starting at the top of plastics which is what I am involved with and know a bit more about. Although I didn't really intend to make a hierarchy, but plastics are probably more commonly used than the other materials. You will find plastics all of the grocery stores. Bags, rappers, trays, and as we go through this presentation I will focus more on plastics and we would take a few virtual box to the grocery store to find were some of the plastics are used. Also, we used our metals. Aluminum cans are probably the oldest type of food packaging going back to the 1800's and still around today for good reason. They play an important role for certain types of food. I'm not going to talk about metal packaging today but note in the next presentation Mark is going to tell you everything you need to know about metal packaging. Also still around are quite a few paper and paperboard containers. If you walk down the breakfast cereal aisle, most breakfast cereals are going to be packaged with a paperboard outer container and you will find likewise the same for crackers and other products. Glass has declined over the years and replaced probably by plastics more commonly. It has been replaced because it is heavy and it also breaks, but it is still there. You will still find the glass in the grocery store. An important point is the materials are often used in combination and that is probably more the rule than the exception. A simple example would be plastic coated paperboard. Milk cartons you might think of as paperboard that gives it the structural integrity of paperboard by itself would not hold milk very long and it has a coating and it's more in the form of polyethylene. Another example would be plastic bags which may look like a simple plastic bag, but commonly contain more than one layer with each layer providing a functional benefit needed for that particular food. Maybe one of the better examples is potato chips. You probably know they are rather reclusive and they don't like lights, water vapor or oxygen. Paper bags for chips are made to avoid those. The bags are opaque and typically made from polypropylene. The bags are usually filled with nitrogen after the chips are poured into keep oxygen out. The bags often are metalized with an aluminum layer. Something that looks fairly simple can contain multiple layers. Again that is more the rule than the exception. Finally food packaging is an innovative field. These trends we have seen over the years and plastics replacing glass and diversity of packaging types, there is a lot of innovation going on. In a couple of presentations are going to hear about innovation and action. One of the things that Mark will talk about his recent innovation in the can coding field and interesting chemistry and food packaging. Dr. Barton will talk about innovation in her area and talk about some of the information as we go through the presentation.

I'm going to spend my time talking about plastics. You might ask why plastics? It is a combination of reasons, one of which is functionality. A diversity of plastics which can be used to make a variety of food packaging types which are suitable for packaging a wide variety of food so there is a lot of versatility. Plastics can help maintain food freshness. We live in a

country where we have the luxury of having a lot of food. We also waste a lot of food and plastic packaging can help maintain food freshness and avoid some of that waste. With respect to glass, plastic packaging will reduce breakage. There also are environmental benefits. Plastic is inherently light weight so it reduces the amount of material we need to use for packaging. Lightweight also reduces transportation costs. Simply by extending shelf life of food we also reduce energy use because it takes energy to grow and process foods. Finally plastic packaging can be economical so there is a variety of reasons why plastics are commonly used.

Generally speaking there are two types of plastics. The ones most commonly used would be characterized as thermoplastics. Is or polymer materials that can be converted into a finished article by heating and melting them and processing them. The plastic bin cools or solidifies into the finished article. There is a wide variety of thermoplastics out there and quite a few of them are useful in food packaging and we would take a walk to the grocery store from time to time and I will point out where you can find some of these. A different kind of plastics is the thermoset plastics. They start out as a solid material which can be cured into a finished article. You will find these in food packaging and play an important role as a protective coating on metal. Again, Mark will come back to that in the next presentation and you would hear about metal packaging and innovations. Are most sets are certainly not as common as thermal plastics but they play an important role.

This chart I put him not to go through in detail, I put this in here mainly because I know these slides live on so it is for the record. There are a variety of plastics used in food packaging. There is a variety used because they have different properties. Each plastic has its role. It works in certain applications but not so well and others. We have a variety of plastics. They are commonly classified using the resin identification codes.

Those numbers were developed a long time ago to facilitate recycling so think back in the days were if I wanted to recycle a plastic container I would have to sort it myself so it was helpful to know what kind of plastic it was. That is maybe not so necessary anymore, but the resin ID codes are required by state law in a few states said you will find them commonly used. The second reason I wanted to mention the codes is to dispel a bit of the myth. If you go to the Internet you won't have to search too far to find commentary related to safety. You will find recommendations on this plastic “is safe” and “not this one.” Keep in mind the resin ID codes really have nothing to do with safety. In the regulatory role, I don't think you really pay attention to resin ID codes. As an example, high density polyethylene use were milk jugs is also used for motor oil and transmission oil and you might think twice about putting your milk in a motor oil container.

Here is a similar chart getting closer to our topic today of food packaging. Again, I won't go to this in detail, this is really more for the record. Again there are different types of plastics. The one, I will talk about later is virtually all water bottles are made from PET. The same is true for carbonated beverages. You also find it in PET boxes. You also find it increasingly being used in recent years a rigid containers replacing glass. For example things like peanut butter or other types of products. I was skipped over polyethylene and polypropylene since I would talk about those in more detail in the following slide.PVC 3 is not so common in packaging. Polystyrene is still fairly commonly used. In certain applications, you will find it in clamshell containers for take-out foods like sandwiches or salads. It will compete with PET, but you will find a lot of polystyrene and application. You will find it of course in the phone plastic egg containers and also still commonly used in food service items like cups and plates. Finally number seven which really isn't a specific plastic, it is a catchall phrase. Protest mode, if you

see number seven the reason it is number seven because that article is a mixture of plastics so it gets classified as number seven.

Let's focus on polyolefins. Although I show a simple arrow from crude oil to natural gas and natural gas to the olefins, there are several processing steps from the refinery to petrochemical plants where we make the three raw materials that go into polyolefins. The common ones are butene, hexane and octane.

For polyethylene we have several types. We have high density polyethylene which is primarily a polymer made from ethylene. Polyethylene's our primary is our primary classified by density. High density polyethylene, if you have appellate would have a density of typically 0.94 grams. It can also -- low density polyethylene and I will explain the difference between those two. In addition at the link can be co-polymerized with one of those alpha olefins to produce linear low-density polyethylene and low-density polyethylene. All of these are classified by density. That may seem a little strange. Why would density have anything to do with anything? It is pretty easy to measure and that is why it is used because it is easy to measure. You don't have to work hard to measure the density. The density is a get measurement. Polyethylene is a partially crystalline material. High density polyethylene made from ethylene might have about 70% crystallinity. That has the highest density of about 0.94. As we increase the branching in the structure as we add alpha olefins or use a different process to make low-density polyethylene we increase the amount of branching. Instead of a simple polyethylene structure we have branches in that structure. The branches disrupt crystallinity which lowers density. That structure and density correlates with structural and performance characteristics and that is what we care about. Density is easy to measure and it is a circuit for surrogate for what we care about which is performance characteristics. It's Is not the only thing but it is a good starting point.

Perhaps more importantly is crystallinity affects additive migration rates. The highest rate of migration will occur with the lowest crystallinity or the highest character in the plastic and conversely the lowest migration will occur with the highest crystallinity. Typically migration of a given additive from low density polyethylene which has the highest density and highest crystallinity, the migration will be lower than from the same additive coming out of a low-density polyethylene with more density, branching and crystallinity. I don't know if this is true today, but in the past low-density polyethylene had generally been considered as the worst-case for migration from polyolefins.

Let's walk to the through the different types of p olyethylene's starting with high density. High density polyethylene can be a homopolymer containing just at the link ethylene that can contain low levels of it alpha olefin. Just a little bit to disrupt crystallinity which dropped density a little bit. There are obvious examples of high density polyethylene as you walk through the grocery store. All milk jugs are made from high density polyethylene. The cloudy and fairly rigid plastic you will find in milk jugs. You also will find it in big water bottles that are again a little cloudy. And some juice containers, but here we have to keep in mind plastics compete. When I say juice containers, you are probably thinking of is the clear plastic that is PET, but some juice containers, the ones that are OPEC or the single-serve ones are quite possibly made from high density polyethylene. You also will find it in the form of bag liners. In the breakfast cereal aisle what you see are people board cartons, but inside you have got a plastic bag and those are the bags when you try to rip it open is a good chance it will rip abruptly and the serial will fly throughout the kitchen. That is a high density polyethylene bag that is a little cloudy with some structural integrity. You will find that in cracker packaging as well. The copolymer high density polyethylene copolymer, again a small amount, you will find that sometimes and dairy

containers. For example cut cheese or yogurt. I should point out again there is competition between the different plastics. You're going to hear about dairy containers later when a talk about polypropylene so they can be used in competition. That is the common place where you will find it. Also other things like produce bags or some squeezable bottles. What about low-density polyethylene. We have got packaging made with a completely different catalyst and process that inherently introduces quite a bit of branching into the structure. Compared to high density there is a lot of branching and lower density which changes the performance characteristics. Where will you find it? LDPE is considered a good general-purpose polyethylene and you will find it in simple products like bread or sandwich bags. You will find it in other p laces. If you go back to the dairy aisle, the lid is more likely to be low-density polyethylene that has to do with performance and processing characteristics. Another important place where you will find low-density polyethylene is in paperboard containers for milk or juice. The paperboard, you may think of it as a paperboard container, but it's not going to hold milk or juice very long by itself and has to have a coding and that is typically low-density polyethylene.

Linear low-density polyethylene, again there is a difference made by different process. It is basically the same as high density polyethylene with a higher level of alpha olefin copolymer. That increases the amount of branching and disrupts crystallinity and lowers density and it is the disruption of the crystallinity that changes the performance and the processing characteristics of the plastic. Going back to the grocery store you would find it in some of the more heavy-duty bags like frozen food or ice bags. It can also compete with low-density polyethylene as container lids. You also commonly find it as a sealant level. The polyethylene bag might have multiple layers and sometimes the inner layer is a low-density polyethylene and or if there is a sealant layer it will help heat seal the bag to make it easier to seal and hopefully open it. It will also be used in some grocery sacks, again it is not the only one, but a common application for it. Finally in the probably ethylene, very low-density palette probably editing, think of this as low-density with higher levels of alpha olefin. Get more branching and disruption of crystalline and the lowest density but it is the performance characteristics. Going back to the grocery store places you will find this would be places like wrapping or bags for fresh produce and meat and process needs. Different applications, each of these polyethylene's have different performance characteristics and processing characteristics and each one has its own niche where it tends to be used.

We have some ways similar to polyethylene and in some ways different. Roebling can be polymerized by itself to make homopolymer which is the most common. Similar to low-density polyethylene, it can be polymerized with low levels of ethylene skin two ways to make copolymers. One is the random copolymer and the other is impact copolymer. Here is sort of like how density is used as the primary classification for polyethylenes, another easy to measure property called the melt flow rate is the primary classification for polypropylenes. The melt flow rate is kind of a good end in indirect measure of weight which correlates to processing and performance characteristics. It is relatively easy to measure and correlates to things we care about, processing and performance. -- is the most common type. The place where you will definitely find it is the long aisle with all the salty snacks. Potato chips, pretzels, pretty much all of those bags are made from polypropylene homopolymer. There may be more than one layer. The base layer, the primary layer will be polypropylene. It is typically reference to the process by which the film is made. Polypropylene is used commonly and as has good barrier properties. Things like potato chips don't like oxygen, water vapor or light and polypropylene is pretty good after preventing intrusion of water vapor or oxygen. That is a primary reason why potato chips have a pretty long shelf-life.

Trestles and tortilla chips are little less sensitive so you can usually see those. The aluminum layer which adds barrier properties is -- and you will find polypropylene in the form of wrappers for bakery and can be used.

Random copolymer is polypropylene that contains to about six weight% ethylene. This is similar to linear low-density polyethylene by including a little bit of ethylene. The crystallinity of polypropylene is disrupted. For polypropylene one thing it does is it improves clarity. Polypropylene by itself is a little cloudy and doesn't have the greatest optics. By adding a little bit of ethylene and reducing crystallinity, we get better optics. It doesn't have a wide use in food packaging. It still would be found in certain bottles, kind of a soft bottle. There will be some uses in food packaging.

Impact copolymer I think is an interesting beast. It is more of a blend of polypropylene and homopolymer with an ethylene propylene rubber and is manufactured in a single manufacturing process which results in the rubber being funny dispersed into the polypropylene matrix. What the rubber does is significantly changes or improves the impact properties of the plastic is what makes it less likely to shatter or break. Where that can be useful is in products that you will find in the dairy aisle, again going back to dairy containers for yogurt and cottage cheese and so one. Both of these materials can be used. If you're not a graded people staring at you number two high density or number five. They both can be used. Polypropylene would be used because of the impact characteristic.

The same thing is true for frozen dairy containers. Some of those would be impact copolymer. The same thing is true with cold or refrigerator or frozen products where the impact property is very important.

I want to spend a couple minutes talking about additives. Polyolefins, there is a diversity of polyolefins. They are widely used but also dependent on additives. There probably isn't any polyolefins that doesn't contain at least one additive. Usually there is a package included. They are used for several purposes. One is to facilitate conversion of the polyolefin to a finished article. Polyethylene and polypropylene are used in the form of small pellets or beads. To convert those into a film or a container, that can be facilitated by certain additives. Additives improve and use performance and in some cases ascetic properties. Some of the common types would be antioxidants. Primary antioxidants are typically -- compounds but there are also secondary or tertiary antioxidants. Phosphide is used as a secondary antioxidant and they do different things. Primary antioxidants are intended to prevent oxidation from occurring. Secondary antioxidants will help stop the oxidation process once it has started so they play an important role in all polyolefins. Surface modifiers are an interesting one. There is one type known generically as a slip agent. If you have polyethylene pellets and convert that into a film typically the film is rolled up in bit roles. To use the film you have to unroll it. To get to the process the type of material called the slip agent helps to make the film in the first place. Slip pages are designed to bloom to the surface of the film and you can think of them as being kind of a lubricant as the film is produced going through the manufacturing equipment. Now that you've got the role of the film you don't want to go back to a solid block of polyethylene so another type of additive called an anti-block is commonly used. Anti-box increase the roughness of the surface and help prevent the film from sticking back to itself and helps unroll the film so you can use it. Anti-stats, polyolefin films can build up static electricity and empty stacks can help prevent that. Nucleating agents are sometimes use with polypropylene, which it is a bit cloudy. Nucleating agents are additives that help modify the crystallization process and change the size of the crystals so it improves the optics of polypropylene homopolymer so you get the performance attributes, but you get better optics. Then there is a variety of

processing aids used, for example that change the flow properties of the polyolefin as it is being processed. You can probably take a whole course on additives. Professor Rubino would be happy to direct you to some suitable sources. I think it is important to note that with polyolefins we be depend on a variety of additives. I've got one minute left for questions, which I can also cover later.

Comments / Question facilitated by Dr. Barton

Thank you Dr. Hentges. I've got questions but I will wait until the panel. I also failed to mention when we went to the agenda slide we will be having a break so it's not one continuous morning of talks. We will have a break after the next speaker from 1030 to 10:45.

Now I would like to invite Dr. Martin Maier. He is currently managing partner of -- toxicology which is an international risk assessment pharmacology and regulatory practice in Albuquerque, New Mexico. He is certified in toxicology by the American Board of Toxicology and received his PhD in toxicology from Colorado State University. I have known Mark now for a while and he's an all-around good guy.

Can Coatings, Primer, and Safety Assessment: Communicating Evidence of Absence – Mark Maier, Sheperian Toxicology, Albuquerque, NM

Thanks. I am a pilot. but it didn't fly year because College Park is a bit of a challenge to get into.

I think it's important to recognize that used to work for Valspar; thus, all these disclaimers that you are looking at are about them. I'm not being compensated for this so that gives me license for fair use of some of the materials I borrowed from the Internet because it is an educational purpose. I am trying to be respectful of the owners of whoever might have copyrighted information but that is what this is all about.

X mentioned the journalist in the early part of the century that said for every complex problem there is an answer that is clear, simple and wrong. One of the things I learned early on coming from the pharmaceutical industry to the packaging industry is I thought how difficult can it be to stick a coating on it can? I don't think most people would know there is a coating on a can and have difficult can it be? I learned it is incredibly difficult and some of the work X did a lot of work on explaining why you couldn't just go out and get a replacement for BPA coatings. What I'm going to talk about is how we act Valspar with the help of an enormous number of other people found a replacement for BPA aced coatings. I'm going to put that in the context of which you have to change something like that in a can and it is a very complex problem and show you how you prove essential the absence of evidence or is FDA says so you can show you're not going to harm anybody. It is negative proven away and very difficult to do so I'm going to show you how we did that.

One of the first things to keep in mind there are two types of beverage cans and they have different coatings. It is a complex highly technological process to make these cans. What we are looking at is the process of making food cans. Usually food cans are made by a big role of metal that gets coded through this complicated process. It is like making cars -- it is not like making cars. You can see all the complexity up there. The primary part we are going to be looking at is the prime coat are and the curing oven and this is a thermoset plastic we are talking about that goes into these cans.

The food can has been around for long time. There are two ways to make them. What is the old way which is to make them in three pieces and weld them up the middle. The side seam is a weld and creates a whole new set of problems for coating because you can't coat it with the same things. You have to put a special strip on that. The other challenge with the food cans is it has to see a from both ends and keep in mind the slide before which showed you coat the metal before you make these cans, these cans when you put them together the coating is already on there and it has to withstand the assembly of that can and all the pinching that goes on so there is a lot of performance required for these coatings to withstand that kind of machining.

If anybody has seen this guy, he is an absolutely entertaining engineer. For those of us who self identify as nerds, you will love his videos. He is done them on the coatings that are going to computers at all kinds of cool things. I think he's up to 4 million hits on this video alone. If you have a chance to see this video, it is really entertaining. Would he would talk about in these videos us out is beverage cans are being put together and how many steps they go through. I borrowed a couple of screenshots from his video on YouTube and tried to capture him in a good post because we knew freeze-frame things sometimes things are weird. This is the first part of making it beverage can. It starts as a flat piece of metal that gets punched out of a piece of raw aluminum and formed into the cup he is holding enter a bunch of processes, it gets built up so the flat piece get built up and finally, you have this more complicated piece called necking. I wanted to point out one of the things he does in this video that is entertaining. He talks about the perspective of an engineer and he will show you how the flip-top on a soda can is two different kinds of levers and how it converts from one type of lever to another as you open it. If you are a self-proclaimed nerd, you will love his videos.

The other part is you have to go through this necking and it is the difficult part it can making that requires a lot of machinery and precision tooling to get these done. They're all done in 11 steps as you can see just to make the neck on the can and that is before the lid goes lead goes on. You can see how they are cramped and the coating on the can should be able to withstand the crimping and pinching and seal the can. He will talk about the engineering and it is just really cool stuff. Here is the beverage can manufacturing process and as I said it is a very long and convoluted process. You start where the metal is hanging on the left-side of the screen. It shows the role and you go through these steps. Each one of those like around two is the necking process. I like the food can were you coat the metal in advance and build the can, the beverage can is coated after you have made the can before you put the lid on it. It goes to this process. The exterior which is called decoration in the interior which is the coatings Valspar makes goes on the interior which is number five and it is circled in red. Then they go through the necking and the flanging and they take these cans and package them up and shipped them ship them off in a truck that was about 5 pounds. You have millions of cans inside of a truck and they are all filled with air so those trucks usually don't have problems with the Department of Transportation.

This is the essence of the complexity I was talking about at the beginning. You can make cans and coat them and put them together, but when you make the beverage flip-top, there is a lot that goes on there. You can imagine having a coating that will withstand being riveted and the rivet being flattened and Visio made by the coating already on the can when the rivet goes in, you have to have high performance materials and you just can't go out and get that. Is a very complicated process and wasn't easy to go out and get a new coating. You've got to get performance out of that and it is very challenging. The coating that goes onto these cans is very tough and has to be flexible and has to withstand impact and this incredible tooling

including some of the beverage ends that have braille on them. There's a lot of machining and engineering that goes into that.

Once the coating is there, and this is one of the things it DA is interested in is what is coming out of it. Whatever goes in there, the material and the plastic is going to start leeching molecules. I will talk about this in the context of BPA. You get the migration and then you get this kind of output from your chromatogram so there is a lot of stuff that comes out. It is difficult to identify what all that stuff is and I think FDA is always challenged by trying to understand what the petitioners are trying to tell them about what is coming out of this can.

[Captioner has been disconnected from [Captioner has been disconnected from audio]

Here he is with the BPA -based epoxy did for you. It worked in everything. It worked and everything. It is strong and flexible and is impact resistant and has incredible performance and adhesion. It will stick to metal and stay there and that is a high demand material you have to do that particularly across the entire spectrum. You got the beverage and which is the worst-case scenario. You got the beverage body and all of these food uses with different cans and the machining and the rolling and the ironing and then you have orphans like the closure. If you look at alternate materials available other than the BPA epoxy prior to what I'm going to tell you about now, this is the choices you have. You have acrylics, different generations of polyesters and they work sometimes but as you can see with those arrows the red arrow says you can't use vinyl on the beverage and because it will not withstand that kind of machining. The yellow arrows work okay but maybe they don't get the shelf life you want. Each one of those arrows from each one of those materials probably takes three years to develop. If you try to cover all that space you're going to be doing it a really long time. Most of the alternatives to BPA out prior to what I'm going to show you next were sorted in the olio acrylic space. Each one of those arrows took a long time for the coating makers to develop. There are primarily three coating makers. There were only about five people that make these things.

If you have a wish list to make this new coating that is going to replace BPA, what do you want? The list is fairly comprehensive, long and somewhat challenging but you want epoxy performance. You're not going to be up to get an olio or an acrylic or some other polyester material because otherwise you will be doing those arrows on an individual basis. You need epoxy and non- estrogenic monomers. The estrogen hazard as many people concerned about potential health effects. -- the conversations don't end well and we do like [Indiscernible] .No estrogenic monomers particularly if you're trying to get that apostate chemistry out of it. Total migration, you would like to be very low and in this case the target was -- which is what FDA likes to see a something below that for total migration. We would like to have specific migrations for any of the monomers of interest especially with what we replaced BPA with. .5 parts per billion, I came from Pharma and pharmaceuticals -- when I told them we were worried about the health hazards of .5 parts per billion they looked at me that doesn't even qualify as an impurity in the drug. This is a really different world than pharmaceuticals and we had to get very low migration on these monomers. Valspar was able to get an order of magnitude smaller than that on this particular molecule and its related molecules.

If you are pharmaceutical manufacturer like where I came from and you want to make this molecule, who of God a billion-dollar development drug. You can do all kinds of crazy chemistry to make that thing. One of my clients literally brings in tankers of methylene chloride as a solvent to make this pharmaceutical. As you know it is highly regulated but if you are were in the former world you are exempt from that because you are not duly regulated. If you're going to make a can coating you got to pull it off the industrial self and make it in big reactors

in large quantities so that is a big problem, finding industrial scale materials. Then you have to have acceptable cost and that turned out to be an enormous problem as well.

Valspar is I would say very unique in that they were willing to share openly the chemistry in public venues, not only what the polymer is but what goes into making the polymer. It is industry-leading for sure. I think we were pleased we were able to do that. If you're going to have intellectual property protection and go through that process, why won't you share it? That is what intellectual property protection is for Valspar's position was these things need to be shared and it was the right thing to do. This is the molecule right here. I showed this before when I had clearance from Valspar to do this. That is the polymer. As you know, the CFR list, there is the list of stuff you can u se. The problem was there is nothing in that box that was going to meet the requirements we had to come up with this new molecule and this new coating so there was nothing in this box which meant new molecules. Whether we built them or figured out a way to scale them up to industrial levels. If you haven't thought about monomers and polymers, and most people haven't. There are very few toxicologists that say polymers are safe. That is pretty much true but there are certain attributes of polymers that becomes critical when you are trying to develop a new one that are toxicological irrelevant. Monomers make polymers. Everybody in this room knows that but here is the challenge. The challenges if you're going to have a monomer that will react with other stuff, it has to be reactive. Chemically reactive substances also have talked to logical liabilities because they will react with human tissues or animal tissues. You have this tug-of-war because the chemist says I can make this and this and put it in a reactor and get rid of the heat. I can make these fantastic polymers because they are so reactive. Are you really going to be with to use that. This is a huge problem and I've used this slide forever but it's really critical to what is going on. What you would like to have his molecules is molecules that react to each other and physiologically do that. You don't want that to happen. Some of you heard this story, the first time I showed this I was in El Paso Texas of all places and I put this up and I looked out the window and five, here we are. We are in the middle of nowhere. That is what you want the molecule to do biologically.

The question then becomes what can we do about BPA -based epoxies we can use to design a new molecule and process and polymer that is going to replace the BPA -based epoxies. If you look at the epoxy chemistry, this is the way polymers are made, you start off with phenol and reactive with acetone.

Essentially you start with a phenolic compound and you create the methylene bridge in the middle. Then you react with the choral hydrant to make this thing is called a -- either and you need to stick these two together. The important part to recognize that is what we were after was to say this is estrogenic in vivo. We’re not going to fight that battle and were going to come up with a solution that will replace it. The other thing that is interesting about the synthesis is you've got two sources of B PA. The BPA you make and the process of the first step which is making the best funnel and the first place. In the case of BPA you go back in see you make the intermediate out of BPA and you put more into react with the intermediate and get the BPA -based polymer. As it turns out the second source is where all the migration comes from so whatever BPA is coming out of the coding is coming from step two. For all practice will purposes the step up one you can't detect. Here is the tricky part. Remember I said we have to have epoxy performance. That means you have to have the part that is circled and that is the -- functionality. You have to have those -- or the stuff will not be flexible and you have to have the hydroxyl groups or the stuff will stick and without that you do not have epoxy performance. As it turns out those two groups in the middle don't matter much.

There was an animation but I got tired of looking at it and fighting with that. One of the things we did that Valspar was we have to have the four prime capacities functionality. Why don't we take a library of molecules like that we think we might be able to make a polymer out up and figure out a way to screen them without sticking everyone of them into an in beach or assay. It was so simple it was ridiculous. We built a model that would do equilibrium modeling and shake the molecule around until it reached its lowest energy phase. If you can find the molecule that didn't flex in the middle, all of a sudden you had a can because it wouldn't fit the estrogen interceptor. The simplest way of thinking, this is not about electrons but about geometric configurations, if you have a molecule that can fold in the middle is going to be able to flex itself into the receptor that otherwise has the attributes you need. We look for molecules that didn't have that flexibility. I will go into the details of that because it is fairly time consuming. This is essentially what I was showing you before on the left we take BPA and make an intermediate and put BPA back in and make the epoxy low. What the Valspar idea was we don't necessarily have to put details in we can make the intermediate out of the X and put something in completely been is no estrogen liability whatsoever as the intermediate and react those and create the polymer and here it is. If you have ever said I wish they would tell us what is in it, here it is. This is what we did. We started off with -- and some phenolic compound.. You make this thing called bisphenol F. This molecule doesn't fold; it’s almost stuck in space. You don't get the alignment to fit the estrogen receptor. That is reacted to make some smaller pieces of the same thing so you end up with the -- if you want to keep your workers being exposed, there is always the worker side, if you want to keep your workers from being exposed to dust you make it a liquid. Not only is it easier to handle but safer for workers. Valspar decided if we make this intermediate thing with multiple pieces of the same molecule we can make it a liquid and we don't have to deal with dust. How about we react rather than with another bisphenol based molecule, why don't we interacted with a phenol, something that is got two hydroxyl groups reacting together, and that is what happened. You end up with this non- estrogenic bisphenol to get the structure I was telling you about ending you react that together to make a liquid and reacted with a phenol and end up with a polymer that is non-estrogenic and has very low migration and high-performance in turned out to be just as good.

Valspar is brilliant and does the same thing the industry does. We know we are doing and we would tell the world and they will believe this. The reality is that is not the way it works. Just because I said so probably isn't going to get you too far in the world of BPA because there is a lot of concerns about BPA. Some are Summer justified and some are not. That is not the debate. The question is how you are going to convince people it is not just a Valspar. There other people that believes this. We started off with two approaches for doing this. One was the prescriptive approach. Into prescriptive approach would've too green screen, a great tool for things that are not polymers. And we looked at the options for choosing assays to get yourself to understand these molecules. I have to cabbie out before I talk about why those didn't work. What you put into something that you react when it comes out the other end is not the same. If you put hydrogen and oxygen together you get water. None of those are the same. It is true with polymers. When you take something like BPA and react with something like -- either what you get out is not BPA. It is a polymer. Different stuff. The analogy here is when you put this together with this liquid you don't necessarily equal that the can coaching. They are all different.

The challenge with green screen is it is a great tool for assessing the hazard of materials that have unique individual toxicity profiles, so if you look at these two, the first green screen some of you have seen this before. You would say that is kind of nasty stuff. Maybe we would want to use that if we had a choice and the second one would be similar. These are two green screens for sodium chlorine which of course is table salt. That was the problem with green

screen. We are going to look at the monomers but the monomers aren't the final product so that is going to be hard to do. We didn't say we were never going together, let's work with green screen folks to figure out a way to improve their screening process to include polymers and that is what Valspar did. They had a green screen practitioner working with the green screen folks to try to do that so that was another way Valspar was different than others. They wanted to play rather than fight. TiPED, they even say it in their materials is you really can't prove anything until you get it into the animal. Do you want to go to the animal first, go to the animal first and then you can avoid the other stuff. The problem with TiPED is there really is no easy way out of that circle; particularly with a polymer. We decided none of those approaches although they are valuable for some kinds of uses particularly with individual substances that they were somewhat challenging for assessing polymers.

The prescriptive approach wasn't going to work and we had to come up with a different way to do this so we decided, wouldn't it be nice if you had this vision ahead of time and you went to these steps and did this. We started talking to people and started saying maybe we need to be talking to some of the people that are going to challenge us. Maybe we need to talk to the people we are not comfortable with. Maybe we need to ask them for help and that is what we did. This is all the toxicology, this is all the stuff we did on the monomers and the intermediates. We decided to ask for help. It was like the amazing after having been in the industry for so many years and having management that just wanted to fight everybody, they wanted to fight everybody. Valspar had this idea of why don't we just talk to people and ask for help? Don't going like we know everything. Why do we ask these folks to help us? One of the ways we did that early on, some of you may know X from various settings, she and I had a professional relationship before and I said we need a chaperone and someone to help us navigate this and would you help us navigate and take us to the people that can prove us wrong. We want to go to the people that can prove us wrong. If they can't prove us wrong. Is a natural corollary to that. She is that at some an endocrinologist and the scientist so she helped us navigate these waters. These are the folks we talked to. The first place we went was tops University where Dr. Soto is. She has come up with a lot of data that would make you concerned about BPA. We figured it Dr. Soto can prove us wrong then we have a good that went into these universities was done as unrestricted gifts so the money was given to the University and hands off. At that point there was no way Valspar was touching that money and they could draw on it however they wanted to and we got back to them when they were comfortable talking to Valspar. You can see the regular folks down here. FDA is one of the best organizations of the world to work with you have solid science and clear guidance and communications and we can talk to you. It's fantastic to talk to agencies. The X which is the French group, you have to go through this directorate General and it takes forever to get through these. Health Canada you can talk to. I won't go into all these other folks. I do have to make a disclaimer here, just because they are listed. Does that mean we have got an endorsement? There is no endorsement and these are folks we shared with so they didn't necessarily agree with everything we said or did.

Finally we had yet to publish it. Again go to the critics and the people most capable, not most likely. The people most likely to prove me wrong may or may not know the science. This is the article we published in environmental science and technology in January and it talks about the evidence of absence. How do you show evidence of absence? It is not evidence of absence. Count the bodies, you inferred that. . Scientifically that doesn't make a lot of sense. Absence of evidence and -- in the case of bisphenol, Dr. Soto in her work found out it was not estrogenic. Again when you do this as an industry need to be hands off. The best way to do that is to not have confidentiality agreements. Give the money to the University and Stanback and let them do with there good at doing which is to be good scientists. Be selective in who you choose.

The other part of proving evidence of absence is to go beyond what the regulations are telling you to do. Go beyond what the EPA guidelines are telling need you to do on endocrine assays, and that is what we did with guidance from Dr. Matheny who was a solid endocrinologist. She said what you should do is get mammary gland tissue in rodents when you do your assay. We are doing the road and assay because we have to because the regulators want us to use the animals. Let's get everything we can from these animals so to go beyond that. It is already there. Dr.Matheny went to the commercial lab and taught them how to do these amounts and the assays for these tissues.

Again, go beyond. I have got to give Dr. Matheny credit for this one. Why don't you test what is coming out of the can wax you got all the data going into it, why do you test what is coming out. This is the first time anybody has tested the migration stuff coming out. We extracted the cans and concentrated it which is a very difficult process and I have to give the guys that Valspar credit for pulling that off. You've got stuff coming out in parts per billion and somehow you got to accumulate another that to test it is not a trivial matter. And Dr. Soto put it through her same screen we put the other materials through. I believe these are references so here we are; including, Tom and Ronnie at Valspar and everyone there. They are a bunch of technical people. The food and beverage brand owners I won't mention by name and the can makers again who all contributed in some manner to this, and all of those folks of course and especially today, FDA. You guys are awesome.

Migration and Exposure Considerations – Jessica Cooper, US FDA, College Park, MD

Okay. Please everybody, time for us to begin. Please have a seat. I review the chemistry information that is required to support the safety of the few context substance. FDA safety evaluation is based upon first deriving the consumer exposure and ensuring the exposure is supported by relevant toxicology information. It is those two aspects that come together for a safety inspection with food context substance and today I am going to concentrate on how the FDA determined exposure to the context substances. In this discussion when talking about food context substances and deriving exposure we also have to talk about migration which is the primary mechanism in which a food context substance is expected to become indiscernible part of food. For today's talk I will first start out with a brief introduction food contact notification and talk about some of the information that is needed to support the safety assessment. And then I will get into FDA assessment of migration and exposure and then really walk through an example for you.

So within the center of food additive safety and applied nutrition the office regulates and conducts a premarket review of all food additives and as Doctor Adams had discussed we have different types of food additives and this responsibility is really separated into different divisions. This is a really broad organization chart of our OFAS . We have the division of petition review as well as division of biotechnology and division of food contact notification. We have these broad categories of additives generally recognized as safe substances by technology and food context of not taste substances. These all fall under food additives. These additives tend to be what we would think of as food ingredients and that of course there are food context substances which I will be concentrating on.

Doctor Adams doesn't like our definition so here is a definition for you. “food additive is all substances the intended use of which resulted may reasonably expected to result directly or

indirectly in their becoming a component of food or otherwise affecting the characteristic of food.

This definition really covers both direct and indirect food additives because of this main phrase may reasonably expected to become a component of food. This definition was defined in the federal food drug and cosmetic act. Around 958 to around 1958 all food additives was conducted to the food additive petition. I think you automatically think of direct food additives or ingredients tastings that are added into food like sweeteners or emulsifiers. The thing that they don't necessarily think about is the indirect food additives.

So in 1997 the food and drug administration modernization act defined a food context substance which is an additive but is substance intended for use as a component of materials and to be used in manufacturing, packaging, transporting of food that is not intended to have a typical affect and food. The food and drug modernization act established this food contact notification program and I have listed here the website where we have the list of affected food contact notification.

So let's talk about what are some food context substances. When we talk about food context substance going back to the definition then the component materials contacting food is when looking at our going to the grocery store or really looking at anything that touches food, we immediately think of food packaging. We have our bottles, paper, boxes, plastic bottles, but those are really food? -- Food contact materials and then the materials that contact the food will be things like metal coding, paper coaching, and adhesives. And I brought some items that I could show and tell. When we think of food contact we think of these bottles but also when we open up the lid there is going to be contact with the lid. These are all food contact materials. The other food contact materials that we do not think about is things that are used in food processing these are filters, lubricants, conveyor belts, antimicrobial agents. Within the food contact materials we then get really into what food contraceptives is “a component of a food contact material” or “these are discrete substances”, and when FDA reviews these, these are reviews of a discrete substance and not the whole packaging itself and examples of food context substance would be monomer, catalyst, polymer, additives,

The meal uses dose as the main uses of the food contact notification. I know Doctor Adams talk to some of these days just three feet. Has 120 day statutory review It. These aspects differentiate it’s self from the few food additive petitions. And on the notification notifier must demonstrate that the food context substance is safer intended use. It is a data submission basically and what it looks like is we have FDA form 3480 which has really a checklist of information but it also has to include relevant supporting information and that includes regulatory information, chemistry, toxicology and environmental. This is when FDA does a fair evaluation of the data. All this information really is supporting the safe use of this food context substance. The regulatory information provides the history of the context substance. They also have food context substances that are used for different uses you can have the same food context substance used in different applications or ways. And the food and contact notification is for an intended use. Also the history can include perhaps the food context substance has already been regulated or another notifier has the notification.

The environmental information goes into supporting the environmental impacts and that is usually with an environmental assessment or categorical exclusion. Now the chemistry and toxicology information comes together for the safety evaluation or the safety assessment. Again as I had said previously, the safety assessment is really contingent on these two aspects 1) evaluating consumer exposure and 2) supporting the invaluable toxicology

information. And for the safety assessment, this is a reasonable -- with no harm. And for the toxicology review, the data that is needed to establish the safe levels of consumer exposure is going to be found in two sets of information that is required in food contact notification and what is the safety narrative which describes the scientific ASIC of the notifier safety determination, and the second is the comprehensive toxicology profile where all safety studies related to the information is relevant to the safety assessment that is provided. FDA has an exposure driven tiered approach for safety's assessment. Basically the more exposures, then more are supporting information that is needed. We really come back down to how important consumer exposure is. And how important it is to fully determine what are the levels. Let's talk about how we assess a consumer exposure to the FCS.

Here is a list of all the chemistry information that is required in a food contact notification. Doctor Adams had a nice light in his presentation really breaking down each of these. Let me walk to them as far as getting you an idea why this information is important and how we actually use this to assess the consumer exposure. First is identity. We need to know exactly what is the food context substance days the discrete chemical name, the chemical substance came to the manufacturing information is used to support the identity. You know when you manufacture, you synthesize a chemical and you can do in many different ways so the manufacturing information help support what is the food context substance. The other part of the information in manufacturing helps support the identifying impurities. What other components come along with the food context substance. Now we talk about the safety assessment of food context substances, we are talking not only of the substances self but of its components. We are talking about any impurities, any residual materials, byproducts, etc. So in the rest of my talk I will probably talk about consumer exposure to the FCS but I am also talking about the composers as well as the constituents.

Setting up where and how a person will be exposed to the food context substance. Often times the food context substance which we had already heard about how Austin and the variety of food context substance materials we have.

- How is that food context substance going to be used?
- Is it going to be used in a can lining?
- Also what types of food are expected to come in contact with the food context substance?

We have technical effects and the technical effect is the food context substance in the material not on the food and basically for this type of information we are concerned about the minimum needed to achieve the technical effects for instance if we have an antioxidant and there was data showing that you have antioxidants let's say 1%. You should not have that antioxidant as 5%. So this is all to support the safety use of the drug days to the context substance. Yes, I have stability which goes back to impurities. Is that expected to break down? Is it going to be introduction of any other migrant that may come into contact with food or become a component of food and then of course the determination, the migration level. How much will that food contact level is getting into food and exposure estimates. That is a lot of information, but really it boils down to a questions and that is what the food context substance is and what has the potential for migrant been and potentially go to be migrated. How much is migrating and how much are we consuming? Everything except the migration is the same type of information that is need for drug food additives. We are still working at identity and manufacturing but the thing that makes food context substance different than direct food items is the direct food additive -- direct food items is the migration. For food context substance the migration is important because you add so much into your food contact material but most of the time that does not mean that is the amount being added to the food.

Going into migration, and futon, and food context substance is easily expected to become a component through migration and the data is assessed to determine consumer exposure. The migration level can be estimated two ways. We have migration testing and we have calculation. I'll discuss migration testing in detail in the next couple five. Let's talk about calculation. The other ways to determine it is one way is 100% migration assuming all your food context substance that you at into the material will get into the food. And often times we don't recommend that because many times that means you are going to have really high exposures and it just does not reflect the actual use. Sometimes 100% migration assumption is used when analysis is really difficult and you really are starting with a very small amount and you can demonstrate that. The other calculation is diffusion theory calculation which is based upon migration modeling which is based upon different polymers and migration to different polymers. Let me get into migration testing. In our guidance we have a chemistry guidance document and within that guidance document we have some regression testing protocols but we recommend for the different uses. In these accelerated temperature and time conditions that are intended to simulate the processing and extended storage. This is consistent with the intended conditions of use with respect to use level, food types and food dish and temperatures. This goes back when I described this long list of chemistry information that condition of use is very important especially when doing migration testing because we have to hope you would want to test your material properties how it will be used. And also we recommend food stimulants. The analysis tends to be difficult with the food matrix so we have food solvents for analysis.

The exposure estimate that we focus on the probable exposure that will result from intended use. In the tent to say that a lot X probable exposure that will result from intended use. Because we are really looking at the intended use of the food contact, if you are going to use a context substance in a frozen bag, then doing migration test with that frozen bag at other temperatures that it does not reflect what it is used for.

The consumer exposure is termed as estimated daily intake with the unit or micrograms per person per day.

We had standard assumptions when we do our calculations. They are done with the highest migration level to be conservative. It captures 100% of the market and all of the diet is in contact with food contact articles. We also for calculating exposure calculations we can refine exposure calculations by using packaging factors. And we have a whole list of this and I will talk about it in a little bit. The refining of exposure calculations is based upon defining the market. So how is food context substance know how does that food contact material be used and how much of that market impact how much of the food contact or food packaging market is it's capturing? We have food packaging factors. The FDA has two types of food packaging factors. We have a food packaging and of consumption factor. When we first talked about consumption factor is the fraction of the daily diet expected to contact specific packaging materials. So for instance if we are taking sort of the ratio of the amount of food that is in contact with the Pacific material are specific material to the amount of food that is consumed in total. For instance if we look at X we have a consumption factor .17 of the polymer coated metal what we are saying is all the food that is package 70% is in contact with polymer coated metal. Looking at food type distribution factor does this takes into account the context of a different type of food. So when we have different foods days we have FDA categorizes in acidic, alcoholic and fatty. The interactions between the different types of food and sometimes the migrants may result in different migration. So this food type distribution factor takes that into account. For polymer coated metal, the food type distribution factor is in this case this is saying of the 17% of food that context metal, 16% will contact with these percentages, and

examples we have aqueous would be your typical canned foods. We have acidic which could be your tomatoes, alcoholic would be our beers and fatty would be like condensed milk.

Now getting to the calculations of the total migration of food context substance, we take into account the different food type distribution and the different types of food and we do a weighted average based upon the migration into these different types of food and then the estimated daily intake is derived by taking the migration and in this case consumption factor times 3000 grams of food per person per day. This 3000 grams of food is an assumption that FDA uses that this is how much one person will consume in one day and they should I do have to say that these consumption factors in these food type distribution factors are only for single-use packaging. And I will talk about it later and I will tell you why that cannot be used for other scenarios.

So let me walk through an example. We have food context substance copolymer and its intended use is in the can coding. And it's intended for food context of aqueous, acidic and fatty foods and the maximum temperature of 121 Celsius. Here we set up how the food context substance is going to be used. Now at this point as a reviewer, the notifier would have already provided what the food context substance is and also the impurities. So in this case for a polymer low molecular weight or oligomer and that is a possible migrant. Also monomer letter a and monomer B in any impurity C from the starting materials or it could possibly be an impurity of monomer letter a or it could be a byproduct of the reaction mechanism.

In this case we are going to look at migration testing. To determine that migration level dish how much of that food context substance in its constituents are getting into food. We have our test sample and of course this will mimic how the food context substance will be used. Which X actually sometimes we don't see this. Sometimes we see coatings that do not mimic. This has to be really how are we going to establish the migration of this material? Coding containments through context substance is impacted by the amount that is going to be used and the thickness that will be used. For now we have food simulate we have 10% ethanol for aqueous and acidic foods and Migliore for fatty foods and the test conditions would be high temperature, heat sterilized or retort. And you have test samples that are heated at 121 Celsius and held for two hours and then 40 degrees Celsius for 238 hours for a total of 10 days. This is an example dish one of the migration protocols that we have and this is to mimic first the heat of the thermal production and then also the long-term storage. When we think of a can, you think it is just going to be heated and then on a shelf for a long parent of time. Well if you are going to test the migration I guess you could say I will take that can or I will take that test and see what comes out after a couple years. Well of course that is not reasonable to test. So FDA had done a lot of testing and allowed us to figure out temperatures to actually mimic that storage. In this case we have accelerated time and temperature to mimic the long-term storage. Tests that are conducted in triplicate and samples are taken into two, 24, 96, and 240 hours to really get an idea of how much that food context substance is migrating out and the test samples are analyzed for the possible migrants. Sometimes we will see test with a look for everything but because we have this discrete food context substance and we have already identified the impurities in the migrants, then an analysis can be geared towards that.

Continuing on our example, we would have the results X. We have the migrant and the migration into each of the two food stimulants. And in this case we have units of micrograms per kilograms. Oftentimes we will see units of micrograms squared which is the amount of the substance coming out of the material per surface area or often times identifiers will convert that into micro grams per kilograms that is micrograms of the migrant and kilograms of the foods you are taking into account how much food is in contact with the material. In this case we have

a food context substance 500 micrograms per kilogram coming out 10% ethanol and 600 coming out of Migliore. To do our calculations just using the LMWO for example we take the factor may glass and multiply it by the point when 6×500 four acidic. .35 again 10% ethanol is used for acidic food as well so that is 500 and .05 point distribution for the fatty. You get the weight average migration standard 309 parts per billion. And again if we were X if this food context substance were be in contact with alcoholic food that would be included here but because it is intended use for these three types of food that is that what the calculation refracts.

Daily intake takes into account the consumption factor times the migration times a 3000 grams of food per person per day.

So we get exposures calculations for all of the migrants. We have oligomers, monomers, and the impurities. And then of course this would be sort of the combination of all the chemistry information is to determine the exposure and that is when toxicology steps in I hand over to a toxicologist and say here you go.

So in that scenario, talking about a can with the single-use packaging there are times when we are not going to use the single-use packaging factors because they are called packaging factors and they are only apply to the single-use materials. These packaging factors were derived by market data. Looking at the market of food packaging, seeing the ratios and the amounts of the different packages there are times when we will not use that because they have said the packaging is not the only type of food contact material out there and it is not the only scenario in which food contact substances are used. We have scenarios where they are not applied which are repeat use scenarios. Examples of that is a conveyor belt, filters, that sort of thing. And the way that we would calculate the exposure to that or the migration from a repeat use item is taking into account the amount of food that is going to come into contact with that repeat use item and the lifetime of that repeat use item. And another scenario is where a direct additive calculation might be more appropriate. Additive we are talking about the food additive and I had mentioned with the information that the chemistry information is the same but for a direct food additive we have a sweetener and for instance we know that we are going to put two sweeteners X one gram of sweetener in a certain type of food then we know that is exposure. And because you take into account the consumption of that food. Well there are times when we need to use that type of scenario for food contact substances when that food context substance is only going to be used with a specific food. I have an example of a microwave popcorn bag or you take your migration and you still have to determine the migration and you multiply it by the consumption of that food and if you recall we use 3000 grams before. But in this case it would be X food. Another example would be using in antimicrobial agent on poultry. Knowing that the food context substance is only going to be introduced to poultry then you can take the migration and multiply it by the amount of poultry meat that one person is going to consume per day. And that information, we use USDA has public information on the consumption of U.S. citizens days how much of certain types of food does a person usually consumed. Another scenario is contact with infant formula or human milk. And that is examples of food contact articles where it is like packets formula and the reason why that -- we don't use packaging factors for that is because we are taking into account only one food source. So sort of like the direct food additive. The example I gave you dates we are going to take into accounts how much food in this case and if it will consume. And then that is how our estimate is determined. So I gave you some brought examples of how FDA calculates migration exposure. All of these exposure substance and migration substances really have to be view case-by-case. When we get notifications we are looking at all of that information and if anybody has any questions, we really do encourage industry to come talk to

us. If you have a situation you are not entirely sure how to tackle the migration or calculate the exposure we have the PNC program that people can come and talk to us. We also have our guidance documents here. Have on our slide so you can go to our website. We have administrative how to get and submit the food contact notification and the chemistry information. A lot of the information I was talking about is from the guidance document. We have toxicology and environmental as well. Thank you.

Online Question for Dr. Cooper

Question: How do you look at potential exposure from things like labeling or printing materials? That seems to be a current issue in places like Europe.
Answer: When we are looking at food contact substances, we are looking at things that are presented. The printing ink and the method in which the printing ink will come into contact with food is usually through either offset or rolling up material. Often times there are some substances just like any other food context substance and we are going to look at the pub about migration into the food contact material. So really you have to have determination of how much of that is going to get into the food. That is really true for anything that will come into contact with food. It will still be based on how we are going to determine the levels. Thank you Jessica for a very educational presentation.

Miria Rubion Introduced by Dr. Barton

Now I would like to invite Doctor Maria Dr. Rubino, Associate Professor at Michigan State University where she has been since 2004. She has over 15 years of industrial experience working as a scientist before starting at Michigan State. She teaches courses on packaging permeability and shelf-life and application of instrumental analysis for packaging. Let's welcome Doctor Rubino.

Packaging Innovations to Improve Food Safety, Mario Rubino, Michigan State University, East Lansing, MI

Good morning everybody. It feels great to be here talking about packaging. Sometimes I don't find a big group to talk about packaging but it is great here we are together to talk about packaging. I am going to be discussing about packaging surfaces. It is really not about regulatory or testing but what is new in packaging and what we are looking at them packaging. And this whole project about the active circuses and active surfaces really did not start as looking at active surfaces. I will give you the story of where it became an active circus development and innovation. Initially because we were looking at silicate materials it was nano place. There used to packaging for many reasons. They are added into the packaging and they are exfoliated. They serve to provide better barrier for example you put X and improve the barrier to a lot of gases. That is pretty nice. Also improve the mechanical properties of the polymer and therefore you need multiple polymers so it is very nice for sustainable surface. Use the amount by 30% or 40% of polymers and obtained the polymer. But the problem was that silicate materials although they are being used, the problem is that nobody has measured how much of this nano-plating migrated into the polymer. So we were concerned. We were looking at all of these polymers that are added in nano-clave and we are not sure what is happening and what the state of this nano-clave is when they are in contact with the food or the additives that come with the nano-clave. So this is one of the motivations that we had. And

from our findings we find something very interesting that during our process of looking at these research, we have further development.

As I mentioned the main reason is to improve the area through mechanical properties and we use the amount of polymer and nano-clays that were used at low cost. But as I mentioned a new study most of the polymers that we used clays and most of the clays that we used X there is many different type of clay with different shape and because they are layered, and again you find it in nature very easy and when you purpose the film and you add it, they become a big platform. Now you can see these are the composition of the clay and this is the shape of the clay. So it is very important for us. Later on you will see why we needed to be able to understand the chemistry of the clay to see how we are going to be able to measure later on the migration. Now why you may think were we concerned with migration? Imagine if you have in this case here would be the film. If we have the film stemming from the packaging and we have nano-clays this food will migrate into the food and then intern it can turn into consumption and or if it goes into disposal and we had the nano-clays migrating outside the film and it could go into the soil and the water and again we are going to be exposed. And then there are other ways for nano-clay to come from other consumer goods. So we were really trying to understand if there was any migration. He did not know at that point. But if there was, there were rows in which we could have exposure. Now you may wonder, why is this a big issue? The problem is that there is X the physical chemical directive because of the nano-particles has a very important impact and help dates health. X impact in health. If you go through membranes so it is very important to characterize that. There is literature and references on the size of nano silica particles that are less than 10 nanometers they could migrate throughout the system or the body and could have health implication. The shape of the nano-particles have impact in the toxicity of the clay. For example the platelets were cytotoxic than any of the other nano claims. Surface area is very important as well. The shape of the nano-clay and how this nano-clay and the size and shape also has an impact and they have done studies. And the aggregation of nano-clay has caused sums toxicity and cytotoxicity. Although I listed these articles and there are much more information for me what is serious about this dish a lot of these studies were done in maximum dosage. And I thought it is very important to understand how much is coming out because maybe it is not so much. So they've found all this toxicity, but all the data that was reiterated was quite maximum dose. In light of that we said okay, first of all we need to determine if nano-clay from the nano-composite and how is it being released? How much is being released and also another important thing is to determine in what shape it is being released. We want to understand also this whole process and how can we model the release? Because we understand the diffusion and the modeling and production, this was our concert. First thing before we started with said okay before we get involved in this process dish it is quite big, right? Let's do something to see if the nano-clays come out of the film are not. So we decided that in order to do that let's label the nano-clay with a fluorescent probe. Let's put it in the film X extruded in the film and make sure the film is exfoliated etc. etc. Let's do some migration days put it in solvent and trap the nano-clays to see if it is really coming out of the film. If it does then let's go into a migration study and do everything that we need to do. That is what we did in the paper. So here we produced the clay. 5% of the clay dish very little in the film and then our first challenge was the probe will survive the processing right? Because that was quite hard but it did and we had a film with which we were able to observe after the processing I still had enough clay that was labeled. And then we put it in the solvent and we took the solvent and we have observed that the solvent sometimes we found fluorescent clay coming out. So this is the way we labeled the clay and actually we patent this because later on you will see we use this again. So here is just a very simple system to label the clay.

Since we found there was some clay coming out we decided to produce the nano-composite, we decided to have full characterization of the nano-composite and then okay let's do migration and we need to do also migration of the surfactant because the nano-clay and in order to add it into the polymer you need to have a certain system that facilitates the dispersion in the polymer. So improve the interaction between the clay and the polymer because they do not like each other. The emollient compounds the surfactant that they are added in the clay. They will facilitate the processes. There we made a melt compounding the nano-clay in the polymer. Then we extruded the polymer and we produce the film. And we use very simple polymer. We use polypropylene and nylon. We used very conventional because there is a lot of information. And we produced 85% in the poly propionate and 95% in the nylon. The clay does not like Polly proper night and poly propionate. And this is a very commercial clay that we used. So we produced the film. We characterize the film. We wanted to see the clay assimilated. If it is not exfoliated we do not have nano-clay. The clay converts into the nano-clay to the process of extrusion. And so we have the necessity to look at how much the clay was dispersed and also by looking at the image we can see that the exfoliation is also very good in nylon and probably proper net. Not so much exfoliated but we expect poly propionate has this possibility. The next process is to do a migration study. We used the ASTM D464 11. We use the filmed area of 100 meters squared. We use ethanol,. The volume was 40 millimeters. We used three different temperatures and interesting enough in the ASTM these glass tubes and they use metal tubes. We had to substitute those because of the method that we used and I will go into that in a few minutes. And we have a controlled sample in celled nano-clay. Now what happens is we used our film with the nano-clay with the ethanol and we put at different temperatures. Every so often we need to take a sample and determine how much clay we have. Now the challenge is how do we detect the clay? Develop a whole methodology to do that. Also we have to be sensitive enough but because I want to have the X from the very beginning. So we have the whole profile of migration in order to be able to have all the information to model the diffusion and the movement of the nano-clay during the migration process. So we needed to develop the method for that. And we found the method here also. And we decided to use X because the conventional they use ITP MS, but this takes long to make a measure. So this was interesting and a clever method was use, we really worked hard for this and we use the graphic and we measured silicone and aluminum at the same time. We know how much silicone and aluminum the clay has and as long as we have the same proportion we are mentoring both at the same time thus, we are measuring both at the same time. We had the validation that this method was very accurate. We needed to develop a whole method for the instrumental conditions. We needed the correlation for the stability test. We did the single migration. We validated the whole method. So now we have our several tubes of different temperatures and so every so often we start taking samples and measuring. And this is some of the data we obtained. So here we have the concentration -- the microgram leader of clay. And this is the time at the different temperatures. So here we have the release from the poly propionate and here we have the release from nylon. Right? So there is a small amount of nano-clay that was released. So very small and there is more nano-clay release from poly propionate then from nylon and I guess the reason is nylon is a good interaction therefore this is good. So dependent on the polymer clay interaction will depend on the situation. Also we used [indiscernible - heavy accent]. We did some service area announcement to analysis of the clay. But overall the release of the clay is very, very small so we have the assurance. We know how the film was produced. We know how much exfoliation we have. The most important thing is that we have this data here. We were able because each measurement was very short and we are able to model.

So the next step if you remember we have surfactant. Surfactants are not very healthy either so let's see how much of that surfactant was coming out from the nano-compensate.

Remember that X I should add that the surfactant is not only one surfactant. Usually each has a combination of two surfactants in each of them. So again we needed to develop a method for these and a method for detecting in the development of the method for the surfactant of the nano-clay. Here is the surfactant. The surfactant X is much more the release of surfactant than the nano-clay for sure because here you have the polypropylene as the temperature increased. And interesting we have the control. The control and measurement here is very interesting. This is the clay along without the nano-compensate. We have a small tube with nano-clay and we put it X how much was from the clay. That was the control. So we could see that the release of the surfactant is much more significant than the release of the clay. We are here with milligrams for leader. So it is quite much more. So we did nylon. Okay. And again we could see milligrams per liter. This was much more than what we saw in the nano-clay, but something interesting happened here. This is the control. Actually my students saying -- well the control releases most of the nano-composite dish go into it again -- three times -- [laughter] so there is much more we need X there is much more release for the nano-compass site from the clay. There is some interaction that promotes the extra release of the surfactant. Back then the next step we have [indiscernible] what we did was we developed methodology to measure the nano--clay size when it release. What happened in the salvage? And we develop and validate the method to look at the different shapes and different conditions the clay is released and how to measure the site.

Now we are right to the point. We have developed a metrology tool. They quantify the nano-particles, we can characterize the nano-particles in situ. We are able to characterize the nano compass site. Once we quantify and moderate release of nano-particles from different components -- we realize the release of nano-clay is very low -- in the PPD levels. The release of the surfactant on the other hand is a little more. So we were thinking -- okay, maybe here instead of a problem we have an opportunity. We know that the nano-clay is building a platform in the polymer. Why don't we build that platform in the property and put it in the surface. So I use the nano-particles as a platform to create the surface. So we also [indiscernible] nano-clay remember when we were tracking in the beginning?. For example it could be oxygen absorber, a bacteria side or many different things. So imagine we have polymer where we add the clay in the surface -- in the coding -- right? And we put this -- we marginalize and we built it inside. Before we get into see if it works or not we decided to look at the fictionalization of the nano-particles for example we have many of these fictionalization's that were possible. So we developed and we decided to develop a surface with specific modes of action using bacteria side on the surface and we identified a coating at that point. Remember this is a group of constant. I do not know if it is going to work or not -- so we use the UV coating. And again this is also published right now. So here is what we did. We used two-seat if this is going to work we used ampicillin. We attached it to the clay. Okay?

We characterized that the clay that the ampicillan was attached to the clay and how it was modified. We watch it very well and check that there is not free ampicillan in the clay and that everything was attached. Then we wanted to know exactly how much of the ampicillan is there so we did some PDA . And we know how much ampicillan we have and then here is the composition of the different components from the data of the PGA. Again we added in the coaching -- we wanted to be sure that the clay was properly exfoliating in the coding so we did the FID. And then we applied the clay in a film of course and we have to develop a metric that this is a combination of ASTM e- 2180 and JI asked the 2801. In order to see if the coding worked or not. And so we did X, we worked with that and we observed that some of the results are here and when we put 1% of the functionalized clay day 60% and 1% we have reduction here. We did it with listeria as well as salmonella. Here are some of the results of this clay of Seminole and listeria. And so we observed that it was significant decrease. So the surface was

really active. We also worked with -- we put future test again because we wanted to be sure that there was no free ampicillan days ampicillan. -- There was no free ampicillan. That was the most important part. We had to confirm that there was no free ampicillan otherwise we would see a different component. So in conclusion we have a novel approach to develop active surfaces. There is two essential features in the design of the active surface where we are using the nano-clay and UV curable coating. We immobilized the ampicillin and there could be another mycobacterial side. And we also developed microbiology assessment to analyze it. And so right now this is being -- we are working specifically in developing other bacteria looking at the coding that is more -- we need to emphasize which is the proper coating. The next set you remember we learned about the surfactant. Do you remember the surfactant is inside of the clay and it is being released throughout the shelf life of the product. Right now I have a team of two students working precisely as we did with the immobilization -- working -- looking instead of having direct immobilizing -- right now the students are developing the methodology in order to immigrate -- first try to find the tube like we did with the structure to look at the release of the active ingredient. And so we are using right now PC 662 look at the release and we are waiting to see in order to model the release. One student is developing the whole methodology, the model for the release and study. While we also have another student working in modeling and designing the best clay that will except the formulation of the clay and how to introduce the [indiscernible] in the clay. In designing the release, they are working together and another group is working and trying to look at specifically the coding X how we are going to have coating that we can have indirect contact with food.

Traditionally, antimicrobials and antioxidants and other chemical compounds are added into the polymer in order to produce packaging so they are adding into the polymer. This is in many ways not so beneficial because you lose half of the materials during processing and also that is not so efficient. Having it to directly on the surface and direct contact with the product is the best way to have the packaging.

And furthermore if you want to put bacteria's in the polymer, there is very few bacteria is that you can qualify to do that because during processing you are diluting half of them. So putting it in the surface is very beneficial. And also another important aspect is that if you put the -- if you add the additives like bacteria side in a coating, the polymer itself would be able to be recycled because you are minimizing the amount of bacteria side that you are using and it is due to the recycle and the process.

So here some other different advantage that I just mentioned earlier and definitely the coating is very important. It has to be a coating. The scale up needs to be well established you can find much more details in this publication.

Questions for Dr. Rubino

Question:
Hello . I am from the FDA. If there is no residual free ampicillan that is not contaminated with free ampicillan and the nano-particles are not migrating. How is the ampicillan reaching the target in the inner cell membrane?

Answer:
This method isn't direct contact with the product. We put the ampicillan in the surface and then it has to be in contact with the product. X in the test here the film here we have incubated with the bacteria and we have a coating indirect contact with the culture. So the

ampicillan would be in direct contact. This is immobilized. The ampicillin is immobilized and there's some functional groups that are working -- were responsible with the side effect. So the idea is to find the bacteria side [indiscernible - heavy accent] assured activity of the product. Remember ampicillan -- this is the proof of concept. We chose ampicillan because of the point. Eventually it will be used for a better -- or another type of bacteria side. This is just another group of concept. It has have more than one [indiscernible]. It is used to link to the clay so it has to have enough functional groups. Once we perceive this X we put inside the packaging and covert surfaces. And we did not know if it was going to work. We were very doubtful like you are. So that is just a proof a point that it did work.

[Applause]

Comments by Dr. Barton

At this time I would like to invite all of the speakers up for panel discussion. Also I would like to invite Mark Feeley from Health Canada and Gina Solomon from California EPA will be joining us on the telephone.

Hello Gina very nice of you to join us. While we are getting situated here I would like to go ahead and introduce our two guests that are joining us on our panel Dr. Gina Solomon who's joining us on the phone this year the Secretary. for science and healthcare California Department of such agency how EPA and she's also a clinical professor of Medicine at UC San Francisco prior to coming to how EPA 2012 through the Senior Scientist that National Resources Defense Council and the Director of the Occupation Environmental benefit from the program at UCSF co-director of the test have pediatric environmental health study by Friday of areas including children's environmental health reproductive toxicity, a cumulative impacts use of novel data streams to streams chemicals for toxicity. She has a very strong educational background. She received her bachelor's degree from Brown University. Her MD from Yale and her miles per hour in her residency and fellowship training in internal medicine and occupational environment to medicine at Harvard. Educationally she's really got quite a pedigree.

I would also like to mention a little bit about Mark Feeley. He is the Associate Director for the Bureau of Chemical Safety Food Directorate Health Products and Food Branch of Health Canada. The Bureau of Chemical Safety of Health Canada is responsible for policy, standard-setting risk assessment research and evaluation activities with respect to chemicals and foods in Canada major programs for the BCS include food additives, food contaminants both natural and anthropogenic food packaging materials and food allergens . Mark is currently the Head of the Canadian Delegation for the Codex committee on contaminants and food the CC CS. Mr. Feeley is a member of both the joint FAO WHO expert committee on food additives roster of pathological and epidemiological experts and the World Health Organization's expert advisory panel on food safety and he's recently appointed as an expert to the European Commission Scientific Committee on Health Environmental and Emerging Risks the received his masters in molecular toxicology from the University of Windsor. Let's give a hand for both Mr. Feeley and Dr. Solomon.

I like for each of the invitees to just say a few words on their involvement with food context substances. Gina would you like to go first?

I would be happy to and thank you for holding this conference and for inviting me. I'm so sorry I couldn't be there in person. I really did want to be. This meeting is fantastic and we had a somewhat similar meeting last fall in California at UC Berkeley some of the same folks were there and participated and it speaks to the significant public interest in this issue -- these issues of food packaging and food contact substances. There's quite a bit of public concern out there that we are hearing in California and quite a lot of interest in the FDA regulatory system. Then also this appears to be a time as Dr. Hentges said particularly rapid innovation and change especially in the food can linings segment. We're watching that with great interest and we freely to relevant laws and related work in California one of them is California's proposition 65 which is the consumer right to know Law and as many folks in the audience may now a panel of the states qualified experts which is an independent scientific committee listed [Indiscernible] is known to the state to cause developmental toxicity that was back in May 2015. The labeling or warning type requirements come into effect a year later which was last May. The state has a limited term regulation in place that expires the end of 2017 that avoids the need to specifically label products but there is a database that many people may be aware of it said P 65 warnings.DA.gov/BPA list and it includes specific information from manufacturers on products that do contain BPA health so they got dates point of the reasons I think that it was notable that many products to be phasing out of the BPA containing polymer. We do not have any data on what they are going to so that is something that we are obviously curious about X interested in and in that regard California also has a safer consumer-products program which has authority over a wide array of products including food packaging and that program received a petition from consumer group in August 2016 focused on can linings and focus specifically on BPA. There have been some supplemental materials also submitted and including a report the public report that came out from that group and some other NGOs last week's deposition is still under consideration and review.

In California in the safer consumer-products program the list of candidate chemicals goes significantly beyond BPA itself and includes a broad array of TP prime to spin off as well as other chemicals that may be in food packaging including a broad array of ortho phthalates and perfluoroalkyl substances. The fever consumer-products program is designed to require systematic alternatives analyses looking at broad range of issues health, energy use, environmental as well as functional uses and economic considerations. We are trying to take a look at what's going on out there and we do have some unique authorities in California related to this topic so I'm very happy to participate in the discussion.

Thank you Gina, it's a pleasure to have you. Mark which you mind sharing with us a little bit about your involvement with food contact substances.

Thank you Chuck. I would like to start off initially by congratulating all the speakers. I think all the topics that were covered in this particular session are very informative and timely because they deal with the main issues that you have to consider with the safety assessment of food contact materials are food packaging materials not only the analytical chemistry but the exposure assessment defining what regulations are currently in place for approvals for food packaging materials some of the toxicology that deals with the assessment of the safety. Then we for talks about it's quite an active and innovative field will obviously food packaging is very important aspect for food safety and what other issues could be facing some of the regulatory [Indiscernible]. From that aspect the current situation in Canada somewhat similar to what FDA has. With specific regulations in our food and drug act and regulations that have a general prohibition about using packaging materials the main part possibly have hazardous substances to food. We do have somewhat a similar association with how a manufacturer can generate and provide the information that can be used in the safety assessment to provide an opinion of

what the except to build a food contactor food packaging material picked then from that aspect we tend to go to more of a positive risk just an evergreen type of document which is somewhat equivalent to an X. I guess just in general -- I think I started with packaging materials early on in my health Canada career and I never really expected them to see the type of public interest that has come about in recent years.

Typically you might even anticipate that the vast majority of the public is unaware except for some minor deviations from this such as BPA and phthalates that chemicals are actually migrating into the food that they consume from the packaging materials. I think that is a big issue that is providing X for the regulatory X to have well-defined and understandable safety it assessment procedures. I think in moving forward there are aspects that would benefit from additional discussion in terms of exactly how the exposure assessment especially with migration studies are being defined as realistic and in new situations especially when you consider all the possible extenuating type of exposures that a packing material might go through under a normal situation. From a talks logical perspective which is typically the area that I have been focusing on I think there's some general understanding that also needs to be further explored such as the FDA is putting a tremendous amount of effort into revising their threshold of talks logical concern and that helps to explain the forest of [Indiscernible] you might get from a typical analysis I migration study [Indiscernible] there some other typically this concept is dealing with single chemicals in single exposures and how you might relate some very low exposure possibly influencing [Indiscernible] or even the exposure assessment. Anyways I think this has been quite an enlightening an interesting session and I think it provides a great deal of information in moving forward when we start to see different innovations in the food packaging field and how they address them specifically from a regulatory aspect and a safety assessment perspective. Thank you.

Thank you Mark. Now I would like to invite anybody that has questions please come to one of the microphones on either side give us your name and ask your question please. If you have any questions online please feel free as well as anybody on the panel If you have questions for anybody else on the panel feel free. I believe Mark has a question.

I just thought in terms of starting off the discussion obviously that people are very eager to start asking questions in the audience. It was very interested in the approach that both partook in the approval of their can coding. Coming through the regulatory quagmire of BPA they should be congratulated into actually taking [Indiscernible] structure as a backbone for their new material. What I had wondered when I saw a you putting up the structure relatively rigid planar molecule was there any additional assessment done of that for potential reactivity with other receptors and I guess the other question was is the -- more specific to the chemistry was there any information to suggest that the methylation of the federal groups might have any impact of the pharmacokinetics of the molecule as compared to say comparing something like PPF to BPA?

There are two questions that I heard Mark the first question was do a look at the interactions of these bigger molecules with receptors, is that when I heard? The answer is yes we did the migration study and then put it into the E screening in which like I think is the first time that's been done . The modeling part of it would tell you in advance that you shouldn't get a response because it just too big and people -- like you said you see it in this nice linear fashion but in reality if you take one polymer stratify spaghetti so it's really not going to be nice and linear it's going to be all convoluted like a protein [Indiscernible] the answer is yes we did study it in these came as everything that came out and saw nothing. The second question was about the methylene bridge with the methods groups that BP has on it. The only thing that tell you about

the methyl groups that they do give a handle for metabolism so if you look at bacterial metabolism of these panels you find that they can actually together and support in that gives you a nice way for wastewater systems to deal with the BPA that they may receive and that's exactly what happened zippers down wastewater treatment. Without the methyl group there appears not to be a handle to metabolize with because there's no place to put the electrons basically and in the simplest case so what the effect is that have on the estrogen us it is far as we can tell very little. Would really affected -- what really affected is the configuration of the parts around the molecule that prevented from folding like a bird. >> There were a few questions online following with what Mark said. Just to try and some that up in general for assessment on [Indiscernible] or endocrine activity how do you consider that in the safety assessment?

I guess it's really a discussion of hazard versus risk and was that done with these?

That's the age-old question obviously that if these struggles with his FDA historically have been a risk-based organization all my academic training was risk-based. Risk-based decision-making is what you do in flying airplanes pickets what to do in managing nuclear reactors is what you do. It is a way to do it however I'm not sure -- so sure that as the general population that people understand that clearly they don't someone has to say well, so Hazard how do you manage Hazard versus the? The problem of vantage of Hazard-thank you for pointing out if there's no endpoint when is enough like you doing drug safety analysis. With drugs to have this benefit of say well, it's a balance of risk. It's risk/benefit another with the patient has the disease and we are going to treat the disease how much risk are you willing to give the patient for taking Metro to manage the disease If you have that trade-off with food additives and things that we eat I don't think people except that trade-off for fairly early on with the hellfire will get a lot of extra and you really had to chase everything is experts one executive but it was a fiery function as it whether it was in endocrine assay like for estrogen the city antigenicity you had to chase all those things that you are never going to get out of the circle and ultimately that's what we did nothing is practical for everything but if you are trying to replace BPA there really was X as a practical matter you weren't going to get away from that period there was a great deal of resource and money spent to address all of the concerns are raised by the experts that we talked to pick the answer is we had to go after every hazard that everybody throughout is rather than doing any risk a stinking.

X given the unique way that the material X looking at what migrated and then concentrating it and doing the test were there other substances that were tested at the same time or other -- was very positive and negative control. OSHA's wondering.

X is usually eat to serious the answer is yes there was a positive and as a negative control? I don't think so but there was at least a positive control because it's all relative response so you have to have that in their so the answer is yes . Was there another question that I was another question if her parents. Anyway whether other things that come out the answer is when you have the migrant you have everything in the one thing I didn't mention was that remember when I have the slight upper hand these are all the criteria that would like to achieve 50 ppm total .5. We achieved the 50 less than 50 it was kind of borderline because when you get polymers there's all kinds of little pieces of polymer there but for starters medicinal was concerned was not detected with a detection level of .05 ppb X because remember it was back up in the sequence of synthesis so it was far away from the files. All of whatever came out was in that assay.

Obviously I'm not ruling out that an oral Maumee produced in the future but there isn't one at this point. This is Mike Dale of all I'm the Executive Director of the Environmental Health strategies set your which is a private health X appreciate the very helpful information today about food contact notification for new substances golfers innovative development of BPA alternatives for the other information shared. Not on the agenda today is what we are collectively going to do about existing chemicals of high concern that are indirect food additives in our food supply in many cases there three months for with in other cases there's exposure's but we know there's a basis for concern with lead in the food supply perchlorate, phthalates, perfluorinated substances and Polly floral alkyl substances in the food supply. Yet because of our -- there's no systematic initiative that I'm aware of on the part of FDA or others to systematically reassess the safety of these indirect food additives many of which were approved 3250 years ago. Absent congressional reform eventually that would happen but not quickly. Isn't this something we should be discussing and working on together. Isn't there more that can be done to systematically look at the existing chemicals of five concern that consumers are being X learning about being concerned about in the food supply today from food packaging materials and through contact materials? Don't you agree we should do something? That is my question.

Yes I do . The issue of post market safety review is one that we are concerned with and this has been tried in the past the problem that we have is is extremely resource intensive and back in the 1970s there was established a program for cyclic review of certain food additives and the review of the safety of food additives and the agency churned through a number of materials and found out that it was eons the budget of the [Indiscernible] to do too many of those things so nowadays I think what we could say we're focused on is that as compounds come up with safety questions we are trying to take those on sort of a tiered level of hazard so that if we have reports of safety problems as a resource permit will take those your views on purple we would like in the future I think everyone would be happy if we could get some more resources to address these post market issues. I think that there is a presumption that we've looked at the materials premarket and so we've evaluated with the safety information that's available at the time and we felt a lot of conservatism sent to our safety evaluation so we feel that for most of the materials are probably safe but every once in a while new science comes forward new toxicology information that needs to be evaluated. So we are trying to take those problems on as they come within the limits of the resources that we have available. Is is that at the beginning we are a fairly small office and most of our issues are premarket but as we have time and personnel available and the funds to do it we are looking into some of these post market issues.

Yeah the idea -- I agree with you that it's very important set of problems are raised that they get a good investigation and a good airing.

I think it would be a good topic for a future [Indiscernible] given that most of those premarket approval were from decades ago the growing body of scientific evidence within the last 10 years that is raising additional concerns. You know it might be useful for a discussion like that to find out in an era of limited resources one of the best methods that you could use to evaluate those materials? There's probably some tests practices that could be discussed this might allow X relations and that the is resource intensive is some of the methods we use the surface think that would be very useful topic for discussion maybe we could plan on something like that.

Thank you.

Thank you very much about that was an interesting question and it also reminded me that I meant to say at the beginning that this is purely science focused we are trying to keep it regulatory and policy purposely avoiding it's not getting into the political aspects of science but let's just keep it as the real science. That question wasn't but I just wanted to go ahead and interject their okay. Thank you.

This is a Sherlock Holmes kind of answer. There's two kinds of data. There are inducted data -- the data with which are used to generate and hypothesis. Then there's the Sherlock Holmes kind of data that says you do it deductively that is the remove everything that isn't and you and up with what is. My feeling -- I can't get out of the circle that says modeling, in vitro, whether it's exposure or toxicology or activity at the receptor is inducted data and that inducted data leads to a hypothesis that you have to deductively proof and I'm improve I don't mean like show absence of evidence or evidence of absence I mean prove. That said there have been historically -- I don't want to point fingers your of course because I could get into trouble but historically most of the hazard data that we've -- I don't want to say be exposed to that the batch was of words. Most of the hazard data that we've experienced historically has come from that kind of inducted data because it's plausible doesn't mean it's factual so to my knowledge -- in my thinking there is no way to go for modeling to deductive proof you can't get there from there. You have to do in hypothesis driven experiment we you and Maxine get the what is. The answers can't that's my view. My view is that you've got have objective data and hypothesis driven research to get the answer otherwise you are just guessing because it's plausible doesn't mean it's a fact and we pay so much of our policy -- I don't want to get into policy and votes -- politics but we basin off a lot of decisions in our life based upon plausibility rather than proof and understandably we have to do that in our daily lives to when it comes to things that have high impact on health and on policy and on cost you can't do that you have to actually base it on deductive proof that's my opinion .

I agree with Dr. Maier, I can speak when the toxicology side only look at the safety of food contact materials are looking for that did the proof the in vivo toxicology. All the other information is considered more of a sporting information you cannot pharmacokinetics give you an idea of what to look at specifically within that in vivo toxicity testing you can have other in vitro studies also suggest you are on the right path look for specific points but we still need that final proof to say that something is safe in the end.

Thank you for the question. Obviously packaging in many ways expense the shelf life and improves the distribution of the product and that is a lot of X if we are certain elements into the package to a extend the shelf life longer that is a benefit. At the same time it's important to look at what type of medications we're doing to the packaging that doesn't make it difficult than for the recovery of the plastic. Trying to decide this active packaging strategies that benefits the product but doesn't compromise their recycling is very important to both things go hand-in-hand in the think packaging could provide X minimize packaging design packaging not only in the material itself but we sign the packaging with accommodation different factors such as if we're some [Indiscernible] or something that will prolong keep in mind that distribution of the active ingredient within the package to understand how much is going to be absorbed maybe [Indiscernible] within the package so in order to maximize the set of the bacteria [Indiscernible] you don't want to use excessive amounts of bacteria [Indiscernible - heavy accent] we can improve recycling of the material and recovering of the material and extent the shelf life.

Yes please. Maybe just to add to that as an agency that frequent has to respond to those media inquiries about the number of so-called that chemicals that tend to be some packing materials. We find the majority of these tend to be more of a hazard-based characterization sub-reports demonstrating that there's a 175 chemicals of carcinogenic reproductive toxicity properties thing is the manufacturer [Indiscernible] in addition relate to the fact that the exposure of those secular chemicals is either negligible or nonexistent so have think once again is a regulatory agency as part of the overall safety assessment that can be more information or more publicly digestive over material produced in terms of this migration of chemicals but in fact benefits If you have Hassett's property for exposure on a daily basis so

It that this is been demonstrated through a variety of processes not represent any sort of health concern.

I would just add that our goal and we want a faster consumer choice. Consumers are free to choose the kind of foods that they want and whatever quantities they want and we have a goal at FDA to make sure that if they do choose the package foods that the packages are safe and they're not going to interact with the foods they are going to protect the foods through the packaging and delivery system from the point where the packages are filled to the point where their consumer opens them the food will be safe and wholesome and not result in any harm. It's just a matter of increasing the options and the choices for people. If you are in an area where you have access to plenty of unpackaged fresh products that's great that there are a lot of places in the US and in the world for that's not an option so package food is the way you get your food we just want to make sure that it's safe.

This is Gina. I would just like to add in a few thoughts because it's really important to think about in both reducing hazard wherever possible and also reducing risk where it's not feasible to address the hazard directly but there is this very wide distribution and exposure patterns that we consistently see in pretty much any exposure study that's done you see these lognormal distributions with some people fairly far out to the right-hand side on that exposure curve with much higher exposure than the meeting or certainly than the median consumer. Obviously from a Cal EPA perspective we are interested in protecting the average consumer but we also are very interested in being aware of those extremes. When example in the food can context is that many Californians have earthquake supplies and they keep the supplies perhaps in the shed in their backyard maybe in the central Valley where the temperatures all summer long maybe close to 100 degrees close to 100°F which is pretty similar to the migration stress tested FDA does but for 10 days and those cancel said there for maybe a year then they swap them out X putting fresh cans one of those levels like? What about people who have certain types of preferences or they may have very restricted diets so we always looking at those issues and wondering whether the assumptions behind the migration testing and the exposure estimates really are capturing that. In that regard I had a question for Dr. Cooper which is I was looking at the standard assumptions than the packaging factors that are used to adjust those assumptions. I guess I missed whether the degree to which the consumption factor captures those high-end type consumers with restricted diets and also I got a little confused in your presentation where you talked about the situations where packaging factors are not used what is used in those types of situations which includes certain types of foods and chronic exposures and so forth.

Thank you Gina. I thought it was very interesting how you pointed out one of the ways is to decrease risk by decreasing exposure the other is by decreasing [Indiscernible] by removing a hazard. My question to you then would be what doesn't have a hazard. Is there anything we can name [Indiscernible] we had a woman who died of kidney failure from eating too much

celery. Sheet celery only celery every single day she was on a celery diet. It crystallized in her kidneys and she died of kidney failure and then in Arkansas a few years ago drink tea regular black tea Lipton tea every single day and apparently he drank like 3 gallons a day he also died of Crystal failure to the kidneys so those are two innocuous things that are hazardous now a woman a couple of years ago; probably 15 years ago now she Drinkwater. She was wanting to win one for children for Christmas so it was a hold your we for a week contest sorry but a drink a gallon of water and then touched her hand to a car people don't realize that several people each year die from water on the brain encephalopathy you got electrolytes in the brain one of absorbed from the blood to the brain that causes brain swelling and people die. More people die from that each year. Water not drowning but from drinking too much each year than far as an oven packaging material at least that can be proven. I just want to point out three innocuous things tea, water and celery are hazardous. But for risk assessment we know that it's not that much of a risk. I really cannot think of anything that's not hazardous even oxygen causes proliferation of type II the most sites in the lungs of neonates when it's administered and hospitals which can of course block long functioning. Removing a hazard I don't know I think we have to look at it from a risk perspective. Thank you I look forward to hearing your response.

Thank you for the lengthy monologues on hazard and risk. Certainly you can't say that there's no risk from the substances that you just listed if you just stated there were deaths from them. Obviously the hazard from the substances is lower and the risk associated with those substances also was lower but there certainly cancel the policy at less frequent but so can be adverse event unfortunately in terms of people's health. [Indiscernible] to the well-established concept of the hierarchy of control or hierarchy of hazard control that is present in many industries and is now something that's in training regulations in California and refinery safety as of just recently. Again, taking from a different fair you can take steps to implement first-order inherent safety approaches which is the substitution of a less hazardous substance for more hazardous substance or second-order inherent safety type approaches which may depending on the context involve lower finery context lower temperatures and pressures but there may be engineering changes that can be made and we seen I think some examples of that and Dr. Mayers recent Tatian where they've really tried to look at those first and second order inherent safety principles in the actual design phase then when you can't achieve those then you start looking at risk and safeguards and so forth which is a perfectly valid approach but I think -- in the context of the hierarchy of control for personal protective equipment is at the bottom of the hierarchy and hazard reduction is at the top of the hierarchy and risk is sort of informing especially as you get lower and that hierarchy how aggressive need to be hazard has a place there and it is something that is worth looking at and asking that question is there a way to do this more safely with less hazard and then if the answer to that question is no then you start looking at the risk. It's the logical stepwise approach that I think is worth considering.

Thank you.

I have a question for Steve Hedges -- Hedges. When I look through magazines -- the public magazines [Indiscernible - low volume] If I'm just flipping through I will find several artful -- particles -- articles [Indiscernible - low volume] .

Leaving can coding aside probably very little plastic container BPA. Most BPA is used to make polycarbonate plastic [Indiscernible] at the durable plastic primarily used in your publications in a single use food packaging for very little food packaging would contain BPA except for can coatings.

Thank you. I had a question and for Dr. Adams. When you're talking about the definition of food contact substances that if this is not intended to have a faithful effect on such a. How would smart packaging to designed to have a technical effect on food be X is it a food contact substance?

That's interesting question is one that wasn't thought about I think when these definitions were written years and years ago the idea of smart or intelligent packaging was something that was not a concept that the time. I think of we had to look at it under the law now we would consider those is more of the delivery devices for direct food additives and so the idea of a packaging material that delivers an antimicrobial say into the food that would be more of in addition situation rather than an indirect additives because under the law the indirect additives is only -- it gets in by accident by consequence of a physical process but is not intended to have any effect to deceptive flipper thinking red little bit. I think the system is perfectly capable of handling that in giving and it's appropriate safety review we just have to mentally adjust ourselves to think of it as not as a packaging material but as a delivery system at least that's the way I look at it. This is one of the things that certainly don't want to let these definitions get in the way of packaging innovation [Indiscernible].

Thank you. Do we have any questions online? Are there any more questions from the audience?

I have one question left for Dr. Robina
I've been interested in MMT for a number of years I've served on various panels for the military. One of them has been with X in particular in X battlefield dressing because it can incorporate their his medications. Work was on characterizing chemical properties and nanoclay but it was primarily on MMT. To think which is on with MMT also would be the same with other nanoclay's such as bentonite selenite to light and how a site.

Clay is not toxic to clay is not a problem. With respect to when we are heating the polymer now the play becomes they know because we are converting one of the dimensions into another scale. That is where the problem is start. With respect to the other ones.

The shape is a very important effect in the toxicity of the nano-particle so therefore usually tubular are less than the X, then the other ones among -- the other claim X to provide that degree of toxicity.

Thank you for everyone’s questions and participation in today’s colloquium.