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Good morning, ladies and gentleman. Welcome to the breakout session on the use of the cerials for food ingredients, packaging, and dietary supplements. Yes, we have added dietary supplements to this program which means we expanded our invited speakers by one. You should have the following handout. The agenda for this meeting with graphical sketches for each of the event speakers and a list of area restaurants. The first and third were in your handout. [Speaker Unclear - Audio Faint]. These questions will also be in the packet you have this morning. The question is also follow the recommendations that you heard from the task force report. We'll present questions to be answered. Mr.Williams will do so for every seven months. They will be followed by Dr. Jon Paul . Dr.Ray Davis with a talk about issues. And Mr. Taylor discuss really three aspects of these substances. These figures will be followed by speakers who have been invited. Attendees are going to want to discuss questions only from the panel you see before you. This is intended to determine whether guidance would be needed and useful in various areas related to the use of no skill materials and food ingredients situations. There will be an opportunity for open mike after these questions four brief questions or comments on material presented here. We encourage you to submit more detailed comments to the docket at the head of the Federal Register notice of this meeting. The docket number is F DA2008M0416. If you have more things you want to present you can present them at you're five for 10 minutes allocated. We encourage you to send them and in writing. At this time of the right to edit its members of the panel. First of all come on my right Mitchell Chesman. And then [indiscernible]. Dr. Cassandra. Bradley Williams they just reorganized. I am not sure of the names. Kenneth Taylor. Dr. Kim Cassidy from food contact notification. Solely to Richmond from the Office of nutrition labeling and dietary supplements. Debra Herman. [Speaker Unclear - Audio Faint]. A couple logistics' before we introduce the first speaker. What will be on your own. You should have a list of restaurants in your package. You should know where to go. Restrooms are located out this door to my left in case you need that's. There will be a full transfer made available under the packet member that I mentioned before. We will try to give a two minute warning for speakers that wrapup. There will be tougher questions of possible says you all have by raffled sketches of our speakers we will go through the lead they about done. Are there any questions care of first speaker is Mitchell Chesman who is going to go through the session.

I am going to go to this a little more rapidly. Excellent. Everything works. First I will be given some regulatory background and discuss some specific allocations. We want to talk and little about the purpose of this meeting. We will probably plops that they will account on questions. We will focus on specific questions. This is a little bit of regulatory background. For the most part food ingredients are regulated another section 409. Is are materials that are added to food have to be generally recognized As safe will undergo some process by the FDA. There are a number of prices eased depending upon the particular type of application. Color additives require free market approval. Among the

process these that we use our repetition processes which involve regulation. There will be an opportunity for public comment and objection. For about the last decade it is a proper process for getting in direct so-called food contact assessment which is also an affirmative authorization process where FDA must determine safeties up material before they parted. But it is a process that does not require the publication in the Federal Register and promulgation of rules before the material can be used. As I mentioned it is also possible to a market food and that its debts if they are generally Bell recognized and saved. While the FDA opinion is not necessary prior to marketing substances that FDA does have the process whereby and issuant can consult and get the opinion of the FDA on their independent determination for the aircraft modification process. A similar process is in place to consult on safety assessment and determination. Just a brief high level overview of some of the types of materials that we have in mind that might come before us are no materials related to the improved his if every food, flavoring cancellation and net of structures to improve the consistency and processing capabilities of food. We have seen better captioning the nutrients. This also probably relates to a dietary supplement. One often noted is the use of the NL particulate pray to produce barrier properties and less expensive food processing of applications that is actually out there are of the market at a low level. There are other applications we have seen to improve properties of fruit packaging. In addition, to in that area of what has been sometimes referred to as intelligent packaging we have had discussions with industry with regard to the development of man as sensors, protection of microbial and chemical contamination of food and also work risibility and tracking of use of food. Just to say where we come from and the state of science we really think calmly from [indiscernible] that we will need to develop a our approach on a case by case basis for these types of materials. We are hopeful that we can make significant progress with regard to guidons based on input today and the future. Let's talk real quickly. Two points to make as far as the purpose of the meeting. First the ultimate fact of we are interested in giving information and data relating to what data may be necessary to demonstrate the safety of men and materials, whether that data is substantially different from the data that we currently receive part through ingredients or through contact materials. We hope that the feedback we get will consider our current guidelines and practices and focus on the need for enhanced or specific guidance within an area of concern. Additionally I think one major issue with regard to guidance development is that FDA has some input on already is the possible need to discuss circumstances under which regulatory status may change due to the presence of nine unskilled materials. Bevies of the Air products that may be on a micro scale but maybe it is no order generally recognized As safe. It might require regulation by FDA. And again that is occurring to be informed by the uncertainties that exist over all with nanotechnology and religion to toxicity and degradation to the existing purpose. Just want to go over, there are a number of ways just echo that this is the beginning of FDA efforts to engage of our stakeholders in the development of guns and the development of our regulatory process is for dealing with this new and challenging technology. There are a number of ways that we help that communication will take place. We look forward to receiving even more detailed and put and written comments for the docket. The package is open until October 24th. I once emphasized relate to our industries takeovers and the audience the possibility of communicating with FDA through added to master files. We have urged our industry stakeholders for some time to have a free market discussion and

solicitation with FDA to use that capability and provide FDA with up front information. I want to emphasize that there are possibilities for depositing of information on confidential commercial products that are under development and master files to utilize a FDA as the consolidator of that knowledge to better form or guidance and better inform our safety assessments in the future. To cover real quickly that general questions really we are asking whether there are characteristics that raised you need the safety questions and what assessment tools there are available in used in particular by the industry and how practical these tools are from the standpoint of economic and scientific terms. It may raise additional safety issues and provide challenges before us in decision making. The final three questions again are the particular aspects about the product formulas and ore processing that can affect the product's efficacy and/or the safety of the final product. What is your experience? And this is really directed to all of our stakeholders. This is from our standpoint of to get the input on whether and why they have not used materials in their products as far. We also want to know what their concerns are from the standpoint of safety, utility, and perception. Finally any additional questions including stability. We the stability of an issue with regard not only to the material in hell it is produced and marketing but also help testing is and how relevant to the safety testing it is. Specific to the matter specific questions about the packaging can you identify specific components derived from the plans raising or not raising unique safety concerns and why. One of the points made earlier was that one of the test car's conclusions was that nanomaterials to not necessarily raise questions for that matter in relation to other material or through contact material. And one possible approach detect guidance development and the purpose of today's meeting is to get input related to catalog development. It is to begin to identify those areas where we can be explicit about additional safety testing requirements over age was about a lower level of concern with regard to the types of materials. And that obviously as with all guns is the focus. Our resources to be most appropriate religion to public health. The second question, in your experience what analytical methods and tools have proved to be most useful to you in characterizing and skill materials. Can you look into the future and develop methods? These are posed from the facts that often a starting point for specifications or limitations and test methodology for substances that and the Arab press that approval when for that matter substances that do to this program are methods that are used by the industry to verify that material has come to need some sort of a could manufacturing standards related to the efficacy. More of the challenges with regard to Dennis Gill material is point to be thinking critically about those particular to characteristics and controls that relates to the technical specs and considering also FDA and the industry have those characteristics may impact human health assessments. The third question, what physical characteristics of through a related in and of materials are of the greatest concern? Again, we need to leverage as much as possible the knowledge that we have. We want to utilize our space -- sorry, I have to keep up here. We need to as much as possible leverage our knowledge base for what we know about the toxicity of substances and build upon that to extend it to areas where it may not cover new and unique materials used by nanotechnology. Question number four, that has killed food ingredients may behave differently. For example they may interact with other components of the food metrics and entrenched in the human body. What methods are you using to characterize them a skill materials following suggestion? Our concern with regard to -- with regard to of food

ingredients, the following is what the consumer is most exposed to and can be a more challenging area in comparison to a dust medical product where we had to it does a regiment. It then a technology that a different spin on that with the notion that if men and materials are used in food or food packaging those materials may, in fact, be altered by the consumers exposure to them. Question number five, are the current toxicology poorest used for food ingredients and packaging components point to describe the decision or must new accolade's be considered? Are you aware of a suitable test not presently in use that may be more suitable? Are there tests that could be used to reach data on Becker's kill ingredients? Again, I but it emphasized that as we do in our taxes to the guidelines they always maintained that option to request potential and unique to Texas to the data for the safety of individual approvals. And I encourage and the forward the idea particularly weakened overlooked a challenging area incorporated and the tax is the essence of a scheme so that aren't going results can be informed. The next step in the process and a final conclusion. Question number six, is nanotechnology applied to food packaging protection? Poorly such compounds in hands. I have a computer in front of me. What of the perceived impact on the regulatory status or manufacturing perks? Then I would emphasize at this question the this must be practiced by the industry in reaching decisions with regard to registered -- regulatory status and substance. Changes and get an unfair trade practice and a density as raw as changes and toxicity can clearly impact concordance of your material. And the last question how can FDA better communicate issues of regulatory status and safety of food ingredients and packaging components derived from nanotechnology to the public and industry? What does that mean for guidance? I'll give this part.

To we have any questions or comments from the panel? Think you. Of our next speaker is the actor Brian Williams, manager of vision of diapers for an programs, Office of additional products, labeling, and dietary supplements. He introduced the question that was addressed during this session.

Good morning, folks. Could morning, everybody. I am from the division of dietary supplement programs. As you can see, I brought some colleagues with me from the original schedule for this there would have been six of us with Mr. Shultz. That might have been all. I'm very grateful to our colleagues to have included as an their session. I have three questions for dietary supplements. The first one is what data is there for dietary ingredients and new properties are characteristics with additional absorption, distribution, or safety data be needed to demonstrate the safety of men and skill versions of an existing diet care premium? This ties into one of those things that Doctor teeseven discussed which would be the use of the glut of Detroit Master file or dietary products that they would consider. We have discussed and we don't know how we can use those because with our new manufacturing practice for dietary supplement the dietary manufacturer is responsible for complete compliance of the ingredients used in their products. They would not be able to steal information from their customers. The customer would have to be qualified by the benefactor of the target. And finally what data and information should be considered in determining whether a net unskilled version of an existing dietary gradient becomes a nude dietary ingredients solely because it is a man is killed. This is all very new combustibles although some of our people have

expertise in dealing with small particles. We look forward very much to the presentation. The key very much. Questions from the panel? Division chief of the service division at the National Institute for Standard and technology. He will talk about issues the nanoscale level.

That seems to work.

Thank you.We are looking at the questions. A & to address chemical measurement methods. This is where you talk about size. Size does matter. They have not a counter did yet with food additives, but in other areas a very specific size between 10 and 28 managers. So it is not just less land. There are things that relate to that are very specific in addition, it turns out that Shipp matters. Particularly in the news and how to shape the carbon anode tubes affects their toxicity. So as we get into it I am not going to discuss those, but some of the methods would be obvious. That ship as low as chemical characterization. Until we address questions to 3:00, and for. The real crux year is we are trying to say there are recommended methods. What I'd like is what methods you are using to characterize materials and then the human body fell point digestion. That is a tough question. We have seen evidence where as far as every test we have run two different materials or the same materials as far as we can tell chemically are produced from different batches have a complete difference in how the effect organs. We maybe don't know what the differences yet. I cannot tell you what the critical area is. There is a lot of difficulty in characterization. I will give an overview. We can get some answers they kill insect matrices, biological matrices. They are fertilized differently and tasks differently. Things become much more difficult to characterize. I am calling to address chemical characterization, but I'm going to do it into areas. O First dispels bulk the chemical analysis and then talk about special resolve. Polk chemical analysis, we can analyze a sample. It is usually fact. That test could be done for a large amount of material. What it does not do is [Speaker Unclear - Audio Faint]. What exactly is a story on with that material. Hell it is finalized. How much of it is a fictionalized. The have both of these. Let's start with this method. This is the mass spectrometry. If we look at a mass spec you are basically -- we are doing is looking at a piece of the pack rat. We will have a specific class. Some were out and that to hundreds. Usually we will charge upon the negative. A lot of these materials we have to be careful. If we use a very high energy in that it didn't look have done is come up with a litany of what I called the hyphenated techniques which is what we call them. We have different methods of ionization. Some of them are softer and more easy on the French allies materials. We can something into a mass spec. We can do and assisted whizzer absorption. Very solid technique for material. Or we can do an electro spray which is also -- all of these materials, it is the way they are analyzed. They have a function on its routes. So basically this characterizes the range of metals and several on metals. So it is a very highly sensitive technique that we used with these different ionization methods. We collectively have three behind that. We are continually selecting where we are looking at. And so it is very get at determining things like purity of material per cent, even in its truest sense that is a very dead. I can analyze and elements. Moi soft ionization, protein, leverage organic molecules this is basically a very good. We put that in the mass spec. Optical emission, we also have others. We have optical emission spectroscopy. We are great to-did that. I woke up of that. Then I get a

high precision deter aggression. That was done by this method. And we have some other methods by this which is not spectroscopic. It turns out that these have very specific temperatures Attalids they come off the surface. It very accurately determine how much as opposed to just random carbon that you have. Silk ion mobility which is similar to a mass spectrometer, we will look at identify very low concentrations of chemicals based upon their migration in the field . In addition, to those toward if you have large amounts you can do X-ray fluorescence. You can look at the principle lecture of material whether it is the tube will what it's crystal structure is. We have a current emission spectroscopy. We look at what has evolved from the added position process. Spectroscopy, I'll show you eighth of all on that. Carbon data to what you read this apple and a field. I will show you about that. And then we have surfaced spectroscopy. If it enhances the ability to at the eighth by as many as five orders of magnitude. So that is spectroscopy. We actually look at that sample. The to give you a clue to review of these single well, and data to visit turns out we are looking at stretching and spending. The load is unique to settle a carbon atoms. The double up here relates. We can do a sample then determine the purity. Fuel flow, as I mentioned we will basically follow through. So we can certainly do the dissemination. We can also to hydraulic and thermal flow as we get an idea of the ethical problems. That method is being developed now. Differential dynamic light scattering, and this case is used primarily for its size. If you do it in an electric field kit you will have some indication of the source. That is important because of the charges carry together so that they aggregate very rapidly. Or you could determine when to do that and you could modify material. Based upon these measurements you can determine what the likelihood is to fire it. Okay. And of. These are all techniques that give you characterization's of a large portion of the sample. They are rapid and very sensitive and can be made very specific. This is broken down into two with three dimensions. As we go from A to the three it gives [indiscernible]. Well, we would sure like to see the whole picture. Instruments are cheap. He put them on a tray or a bench and your kid to go. We can analyze this represents the whole sample. We would really like to spatially result and said this material contains this and the structure for excellences like this. You can guess as you go into a battle trench you look at a much smaller percentage of your sample. You may only look at a thousand. So here's statistics becomes an operation. It still has to be vetted. People are trying to design them that are a bit more automated so that we can get large numbers. We have the have and as Bill spatial resolution. We have to develop more methods for doing that. It would like to analyze for everything. They would like to know where it is with a certain material with the [indiscernible]. So we would really like to get this process into the process control so that when you look at the manufacturing processes where you look at is you can actually get an answer that is relevant to the various materials you are analyzing. So that desire, as I said, we cannot really be some of those. To give you an idea where we are at these are the bulk techniques that is our comfort zone. We are working in this area of the way down it's here which is the diameter size range. And three are really working with new technology and research needed. It gives you an idea of the difficulty. From here to hear the line goes up exponentially as bus costs. So to give you an idea electron energy is one way you can look at it. Plectrons cut through a material and we can relate that with the elements of a composition. Here you see you can also get ideas on whether the material was wracked by diamonds. It is an indication of species. We can do an elemental analysis. This is properly iron particles.

What we are looking at is where this and the inspector can probe. You can see some and is terrible here. So we can determine what is it materials based on -- this is fast for us. In certain instances we can get pushed out of little further with energy level spectroscopy. We can look at filling of shows and the show back. And we can actually get service characterization of his materials. We can look at what goes on and the surface. Here is a profile that with these two. You can see. So you can start to see with the first line and get an idea. So atomic scale, these are just cued up. Here you are looking at the quantum box. This is when nanometer, if you go in on this you can actually see down here, this is resolution. We can see the resolution of these two in electron density measurements. So you can actually get down to a public scale. Keep in mind, that is where everything occurs. However, looking at Phelps is not fact. You have to know where you want to look and what you want to look for because it is very costly and very time-consuming. Okay. So what are some of the pitfalls? I think it is belated. I can see carbon. However a am sitting on a carbon subject. So what question is, is that finalization? The answer, I have to find another way to get this. Electron density is it going to do it. And this very well could be what you're looking at here. I just can't tell you right now with that is. Okay. One more thing we have done, looking at the statistical analysis, this is our yield spectrometry filter. At the goal here is it comes out of core material. What you see is we have a cold coating on this particle, but there are holes. And so saying that article is cold coated the question becomes what can we do. Well, we can do some particles. We've reflected images. But you can see is some of them have holes. Most of them hovels. Some of them do not. You can tell from the ring around here that the thickness and how many air brigade together. So if we look at a summary of theft we can see how of metal particles are formed through normal distribution. We are able to tell you that if. But the amateur is 130. That 95 percent the ship is round with a few exceptions. Tim% inundation of a longer the major access. The material -- the [indiscernible] come out. The thickness is highly uniform. The coating is roughly 13-14 nanometers. So it is fairly consistent. Cold coating is seldom completely intact. You should expect holes at approximately 10 meters. That is physically observed. Distribution is observed with the number of holes and particles. 90percent or intact. And then the size of the holes are independent particle size. So that is basically the type of thing we can do with this. We are working to automate that so that we can do this type of work with this material and get an indication of when you deliver a product and you say it is it cold quoted or a shell or a silver particle or are you want to call that. And so then you go back to what see what happens when we do this with the biological system. We picked a really simple one. This where we will have to go through the expense of [indiscernible]. So what remodeled was a very simple system, rectangle. We have the nucleus here. You can see the silicon shell, and then mounting technique. This is all in [indiscernible]. So we stuck in a variety of different [indiscernible]. We said, okay. If you're going to do an analysis what can we see?Well, 5-100 nanometers single particle clusters happens. They were not calling to in this terrible. And so we have all of these down here. There are another five here. The distortion of. Only five and 10 -- no five and 10. Then you can't resolve 50-nanometer clusters separated by 250. So what that means is we have to come up with other methods to use this type of analysis to characterize biological material. I can assure you pictures. Biological material or soft material or polymers does far into the material that makes it harder to analyze. Okay. The last topic is the three-dimensional reconstruction and projection. This is the topic out of

the New Yorker magazine. We really have an idea of what is going on. Particularly what I am looking to see what it does and how it works and acts in material was that be a foodstuff or whether that be packaging, it's challenging. So chemical 3D information is often required. It would be said about the true nature of what is coming on with metal particles and rearguard with that. First I didn't know whether to put in here because it's not used a lot by than a characterization's. It is in the analysis. We are developing a large number. This is normally done with a discernible. And they now have new sites the materials like chlorine. You can see the penetration of the INS in this case Silicon. You can get back with a 60 stores and later it. Well, that is pretty good. You still have a problem with lateral resolution. Unfortunately it is desirable. I might not be able to let a single function lies before but I can look at a group. He can determine what the flux lines isn't as. You can look and determine which is maybe what I want. And I my even be able, if I can't find it somehow, calculate what percent is covered. Okay. So to give you an idea there are two ways that we do this. Okay. We may not see these. Anyway, what you can do, what we have to do these things, this is an ion beam where we can peel away layers and then do an analysis. We can do that multiple times in automated fashion. The other way is we can tell this through a whole bunch of things. Both of these can be reconstructed. The problem with a you're looking at here is the electron density, when you go to do that with elements I have to worry about absorption of whatever setup, whether it is the electron or extra. So that is that the see of being able to do what I would call see these chemicals. Very highly resolve back to that instrument that share of the single item. And so if you miss the physics you figure out how you select of signals. We can do [indiscernible]. People are using other methods for the structure of material. But certainly for chemical what turned this is still very [indiscernible]. So if we are calling to go back this is what we are looking at. This shows you the structure and size. Keep your fingers crossed. You are a current to see much here. There isn't much to see. Okay. We are doing here is the electron density. And this is the type of thing you could do before getting an idea of helping segregate and now they are obtained. A reader tried to go back through this several times. Now we are determining where those particles are in the larger aggregates. We back it out and no reconstruct. We can pull that thing out in blue. Now we have held fast particle is a rigid in its native state. We rotate and construct. You can see it, pull it out. This is more time-consuming but it does it in an automated fashion. The greatest question is can we do that with electrons. This is involved with how you calculate where it emitted from and how you construct and. If we are lucky this is the type of assault. This is the damage where silicon is read. In this case has been looking at of value its screen. Here we are looking at the Silicon volume with the analysis and purple. We can separate these out and birds and together. The challenge is to be able to do this in a cell or material polymer where you would like to know what the costs of distribution is. Once it is reconstructed we can understand how it works. So in summary the bulk analysis technique are based on old truck traced methods. Such is mass spectrometry. They are very specific or can be made to be very specific for specific materials. This can be used. I am going to do some of the purity of samples at a very low level. And what the major composition is, the main thing is you can use them for control. We don't get how much of it is covered. So basically you divide information on particle basis. The population statistics. If I spent all day at all like at 50 now parts of the whole sample. That is a difficult issue to have to address. We are also looking on speeding up

process up and making it more automated. The two times you saw, this is about 3 million. So they aren't the type of thing you go to the store and buy. Right now they aren't even close to being used for process controls. However, that being said the unfortunately that now world is determined because it is so varied and we see activity in specific size ranges or specifics the deal with an unstructured we're going to need both of these analytical techniques to really answer the question on which we have. So we have to be able to characterize the sample with a spiked metal catalysts that are left behind that are toxic and that type of thing, but at the same time we have to be able to look at it individually and understand what instruction and how much of it represents what the manufacturer actually has for this material. So I wish I could say there was one answer. As I said just the characterization of the material and the biological system, it is much more difficult. Certainly size matters, shape matters. Surface charge appears to matter, but we can't really tell. People look at the same material with a different set of toxicology. So one person found negative to be the most toxic. Since it is really a challenge when we see these types of characterization. Thank you.

[APPLAUSE]

Do we have any questions from the panel? There is one question with regard to an official confirmation. We are going to get to the points where there will be an issue with security. Projections are limited mostly by the methodology. [Speaker Unclear - Audio Faint]

Right know what you're going to run into is [indiscernible]. Methodologies are evolving. It shouldn't be long before you have to deal with -- it may be -- maybe we follow what the electronics say in this. We go after it difficult stuff and you sort of use it to diagnose what that problem is. The automation is expensive as always. We also have a lot of information coming in and we have to have that information on a whole other pocket. We could load up our computer with terabytes of data.

Think you very much. Any other questions? Okay. We have one?

That actually may be a question for submission to the docket. You put up a graph talking about our need for new technology. And I guess one question I would ask is where are you looking at as far as typical foods and applications being considered for development now.

That is a good question for the panel.

Speaking to the microphone.

Okay. Our next speaker is Dr. Raymond Davis, manager of toxicology for industrial chemicals who will talk about some of the concerns. We want to use the wireless mike.

Ray Davis.

Good morning. I am here to talk to you about the safety of nanomaterials and food packaging. I decided to focus only on food packaging. It is part of the general discussion of what we know. What I want to do is turn and look briefly at the public concern and whether or not that relates to material. Then we will talk about what some of the hazards are and how we evaluate those hazards. Are they exactly the same for ordinary chemicals? What is the exposure? Not ready to spend a lot of time on that because quite honestly that is the right to be very specific to that application. There are some interesting tidbits of information I could pass on about the characteristics of nanomaterials. And how we evaluate the risk and communicate that risk. I think that is where the key issue is. Here are some of these uses of nanotechnology within food packaging. I think Mitch has already used a great compilation of information starting from the membrane all the way down to the packaging. Intelligent packaging tells you the microbial status of the concept. The you can see some of the data materials that are used in the applications. The top two really are focused on anti-microbial activities, and the others are barriers. I am going to use a couple of these examples when we get into talking about data. Just to give you a sense of what we know of these particular applications. First let me just review briefly what our concern is. Nanomaterials have some unusual effects or properties, at least that is what everyone says. A smaller size and the surface impact [indiscernible] to activity. Really what we are talking about is increasing surface area. What is on the surface that reacts and has an impact on biological activity. The smaller size means that there is a greater rigidity to move throughout, translocation. Either via the bloodstream or other mechanism. That is something that has always been a concern for nanomaterials from the outset. My gosh, we can find these where they are not supposed to be. And then from exposures that we get from walking around outside with the associated respiratory disease, cardiovascular disease. Does this apply in food packaging? This is just an example of translocation. These are two examples of men and materials that have been tested for their distribution. I pointed out to areas, traditionally those are thought to have barriers to immigration or distribution. And yet we find particles. Why is that? Certainly they are not as a surly for luxury. Certainly maybe it is [indiscernible]. So does that occur when we have all of these materials? Here I said please summarize the content and effect we see. Inflammation of the log very much depends on characteristics. There is a potential for systemic immune responses. That gives an antigen A response. And widespread distribution of the boats Brant or translocation. So that occurs.Well, let's look.Up here is one study in which we look at the acute toxicity. In animals treated with cellulose stabilized toxicologists are kind of a conservative bunch. They find something that works and continue to use it over and over again. This theme is very common for materials.

Please pardon the interruption. Your conference contains less than three participants at this time. If you would like to continue press star one now or the conference will be terminated.

So we don't find a much jealousy with kids. If there is another study in the size, perversive Becker says tapper and you see here only 50 is greater than 5,000.PR10 times lower, at least 10 times over. So that first question might say, comes, that Dennis says materials is obviously more hazardous. You know what, it depends on how you express

the information. Is, we did see this and the kidneys, liver, and spleen. There are changes associated with this particular organs. It goes up. But we are talking about on a mass space. If you look at it in terms of particle members and then look at the acute toxicity you find that, in fact, you could put that data on a straight line. It is not just a matter of advancing the material. It is the number of particles. In fact does not just the number of particles but the amount of surface area. So if one looks at the particle reactivity of phoneticized material for says Micron material you see changes in Ph that are relative -- associated with the size distribution. It is the belief that is what causes toxicosis. But there is a lot more information. What about repeated exposure? Here is an example of the study that was done they have some minor changes in but the rates being set a lower, although the body weight was higher. I am not sure that is a real concern. This is apparently used as a growth in Hansard. They also looked at insulin levels. Insulin stages of a little bit with respect to those, but insulin definitely increases with those. Here is the control. It bounces around.It is probably not a top ecologically significant. Here is certainly a clear response. Here is another study that will assist both. We have [indiscernible]. Again, given the course of four weeks this said claustral in both males and females. This was accompanied by bile duct her sleep yeah. This is the material and his apology. Here chemistry changes. There is also an increase in the press accounts. Only in female rats, suggesting how the results of an accumulation in the kidneys. Perhaps there is a relationship and the effect here. But no affect level was clearly 100 milligrams per day. Since this same group looked at silver inhalation exposure they reported there were no systemic effects of falling inflation exposure, but if you calculate what the oral dose equivalent is it is only about 10 micrograms per kilo per day. So if one were to say that -- again, at first blush you might say oral ingestion is non-toxic inhalation. Not necessarily. So that is one of the pitfalls in trying to compare one exposure to the other. It is not nanomaterials, but it is the fact that the size has an impact. I think it makes it more impacts to do it correctly. South -- clearly these materials are in and the GI tract. There are a number of different experiments that we have demonstrated that they are absorbed from the GI tract. For the most part very sparing. Size does make a difference. As with thermal penetration the coating on the outside of the particle has a great impact so if one counts you can alter the absorption. And what that coating is has an impact. So if it is an acidic environment that will have an impact. For the most part tissue distribution is a very limited the liver, spleen, and GI tract. And did that is actually in line with what we know about injections of other [indiscernible]. We see those in the liver, spleen, kidney, and lungs. We know we are getting some material in. The does reasons to be very limited. From one study the let that polystyrene you can see the amount of absorption relative to size certainly does go up. But look at the relative absorption. We are talking about less than 10%. So a very small amount. Was it gets into the body of course proteins will have the opportunity and an offer distribution. There are some very delicate experiments that have looked at that. This is a protein that is very clearly associated or easily associated with particles, cutting them, and distribution. You can alter gold nanorods. Other proteins have a preferential itself the absorption on to any material. This is like that, the absorption of a series of proteins relative in three different kinds of materials. Shape probably also has an impact. Certainly does withdrawal penetration. As suggested this tape may be more important than size. And I'm not sure whether we have enough material to make any particular generalized statement. From the

perspective of health concerns or hazardous exposure we see that we can observe toxicity and it is correlated with the deposition. It is not necessarily the same as we might see. Absorption is possible. It is it generally they shape -- or size dependent. It could be shape dependent. It is it generally a small fraction. Article coding does occur. They're likely to have an impact on absorption. A particle can translocate following inhilation exposure. This is important. There may be some differences that are due to the median use of exposure. Remember, that has to be delivered in some type of liquid form. Generally we think if it is water soluble that means I can't see it. That is not a chemical definition. Then if it is an insoluble material we will use carboxyl methyl cellulose or sometimes vegetable oil. How that changes characteristics of the shape of the particle is something we don't always know and something that is very important as we go forward during these kind of studies. If you just have insulation exposure and characterization of the atmosphere we have to do the same thing for all ingestion. The exposure, I want to talk a little bit about the exposure. There are two examples I want to give you where we can control the exposure based on the size of the material. One is changing the size of the nano particle and its release from a particular package. The smaller the size the more likely it is that the particle will be released. Another option is how we coat the particle, whether it is simply code or impregnated into the particle. We have to look at these on a case by case basis. In terms of how we evaluate I'm sure many of you know that [indiscernible] is currently validating the particles. Right now nothing has been reported that has not been using a standard protocol. How the results are expressed, that is to say how the amount of material that is delivered is expressed is going to be very important. You're going to have to move away from just expressing the mass per kilo. We are going to have to exert that to particle, surface area. That does not mean that we abandoned that entirely. We have to have some other way of describing it. Given the current protocols they should be adequate, but I admit that has been evaluated. In terms of techniques that are used to follow materials in the body for the most part we are talking about florescence, usually only four dots. Elemental analysis can be a number of different ways. In some cases radioactivity is used for materials, and it is not necessarily there for all. This is something that is new. Spectroscopy has been used. At least there is one phase in the literature when they look at the acceleration. The question is, can that be used for other materials? I know it has been attempted in skin. It does not penetrate, but it is a possibility. It is something we need to look at. Some non-invasive way of following that. In vitro predictive tools aren't fully available. In spite the fact that there are many who would like to see in vitro predictive tools I have just not sure. The current risk assessment methodologies, I think, should be good.

[Speaker Unclear - Audio Faint]

[Speaker Unclear - Audio Faint]

Thank you.

But then that is really a discussion for another topic later on this week. One of the things I think is important is the communication of what the risks are. Nano and technology are good things. Nano is already accepted. Technology is for a lot of it as somebody.

Particles don't necessarily carry that turned of [indiscernible]. There is a recent survey by the ETA that asks a number of consumers would you think about nanotechnology and food packaging purses foods. Their response was food packaging is okay, but don't put the stuff in my food. That is point to be the case for many of these applications. We are going to need some very clear definitions of what the benefits are of these materials. Pre marketing communication is going to be followed better than post market explanation. I think agencies will have a rule. So to summarize safety of ingested particles cannot be determined using some of the current methods, distribution is limited and different than it is for inhalation. The use of nano materials and food packaging can certainly be controlled. [indiscernible] its interests will be important to public perception. Thank you.

Thank you.

[APPLAUSE]

Any questions from the panel? There is one, at least.

So [Speaker Unclear - Audio Faint]. In your presentation that you alluded to nano particles. One was 51 nanometers. Each of these has central distribution, size, characteristics. To what degree do you think your conclusion might be altered?

You will need to use a microphone to answer that.

I think very definitely the conclusions may be altered. One of the pitfalls that we saw is a lack of complete characterization of the particles as they are used in experimental systems. In fact, in some cases the characterization does not even adequately tell us what the particle is they started with, let alone what the guidance is. It is something we struggle with. I think it is something that a number of us have tried to push to make sure that investigators take that into account. It will be sometime, I believe, before we have a complete set of criteria. I know that there are a number of groups of working on that should be. I know that there are some of us who want to make sure that whatever list of criteria are eventually adopted that the scientific humidity increases that and uses its when it publishes the results of studies. We could easily make it mandatory for [indiscernible]. You could make it mandatory for study protocol, but that does not necessarily trickle-down to what happens at the epidemic level because they don't necessarily follow the same particles that we do. But it would be very important to make that happen.

Ray, I have a question. It pertains to some of your comments about conglomeration of particles, and distribution, whatever. The issue -- we have two forms of basically how particles get together, aggregation and glomeration. A glomeration is being less tightly bound. You would assume that glomerated the particles might be broken apart as they move into the tract and more readily observed were as aggregate particles might be more likely to be passed through the gastrointestinal tract and not be observed by the smaller

intestine. Some are you aware of any studies that have looked at that particular aspect of nanoparticle intake?

In terms of conglomeration?

Whether they break apart.

Off the top of my head, no. Certainly it is something that we need to try to identify. This goes back a little bit to Rick's comment and the comment I made during the presentation. I tried to evaluate the state of our official media. For example one can simulate saliva. One can simulate stomach acid. One can simulate GI content. And to look at that conglomeration state under those conditions prior to doing your test might give you a fair amount of information about how whether or not that the material will be observed, how easily it will be observed. To the best of my knowledge no one has actually conducted that type of study.

To you feel that type of testing might be essential and actually looking at overall toxicity of the net of particles? In other words, if you had conventional absorption do you think maybe adding that type of testing do that particular would get us more information?

I think it would help characterize the particles you are dealing with. Whether you include that under add me or just as part of a required characterization, to me either way. But there is some benefit to doing that. Does it tell you anything? Unfortunately if you went through the exercise and you looked at the conglomerations date it still might not tell you if the material is coming to be easily of absorbed or not. But it may give you some hint. If it doesn't it will just conglomerate into one big ball. That will tell you what you need to know.

Maybe a more specific conversation related to your discussion, have you looked at any comparison to macro versus nanoin relation to (indiscernible) since there is some stake information on accumulation for other studies on macro silver?

If not on that. That certainly would be an interesting exercise to look at -- and then again you're going to have to ask the question what species of silver are you going to look at, whether it is elemental or some solvent because certainly there is a fair amount of information on the various salts.

Just kind of curious, are you aware of any studies that have been done testing the ability of these vast particles on a (indiscernible) dependent basis?

In what kind of --

Like as preparation to preparation, I know the issue was raised about how being a different -- let's say delivery system, an (indiscernible) or hydrophobic environment, be able to change moring on and aggregate and potentially affect their activity, so I am kind of following just when these things are prepared, kind of curious if anything is being

done which just looking at a sample and how let's take did he grades overtime or anything like that, because I am thinking about in terms of consumption standpoint, and shelf life.

I am not aware of any, but that doesn't mean it doesn't exist. Certainly for some of the studies that I presented, those preparations were made frequently and long-term stability wasn't really an issue, and but with respect to let's say food content or something like that, I am not aware of anything.

Okay. We need to move on. Thank you, Dr. David. Our next speaker is Mike Taylor, research professor at the George Washington University public health services. He is going to talk to us about his take on regulatory issues. We'll need a IMCC for you. -- MIC for you.

(multiple speakers).

I appreciate being able to speak today. I must admit whether I saw the questions (indiscernible) and talk about the issues and he assured me he was interested in regulatory policy issues, and that's what I will talk about, but as I hope to make clear the regulatory policy point I would make and the issues I would raise about FDA should be doing on that, derived from science, and I appreciate the chance to hear the previous presentations. I would also point out that -- and I am sure it is just a coincidence but this meeting is being held on almost literally the 50th anniversary of the food amendment of 1958. As all of you know, adopted on September 6, 1958, and that's note worthy because that is the statute that continue to say govern what FDA does on nanotechnology, the statute what is adopted with nanotech in mind, but it is resilient, and I think it does provide the sound framework although I think some speakers (indiscernible) what I will talk about a little bit today do raise issues, but I think FDA needs to address. I think the starting point from our presentation would be just to suggest that in thinking about it over site nanotechnology and doing the job is that FDA as a community keeps in mind purposes of food act when it was enacted in 1958, and there were only two broad purposes I think are pretty well documented in legislative history, and frankly in the way in which FDA implemented it over the years. The first and perhaps the most obvious was the purpose of it in the context of a chemical revolution going on in food technology at that time to ensure that the chemicals being used to provide the convenience low cost food that people were demanding to ensure that these applications of chemical technology would be safe for consumers, public health measure, and it did this by establishing the first time the basic requirement that for new food technology there would be premarket testing and premarket approval by FDA, with the beg your pardon on the sponsor on the industry to approve safety to FDA satisfaction. It was a whole significant paradigm shift in regulation of these materials, and it was established frankly a rigorous system for ensuring the safety of new food tech nothing nothings. The second purpose of the statute of course was to Foster innovation. This was explicit in the legislative history of the statute and ex police at this exit -- explicit among other things in explaining the support of the chemical and food industry at that time for this legislation because the assurance of safety, premarketted assurance of safety was seen as part of fulfilling the aspiration and

being able to Foster innovation in food technology without (indiscernible) safety to the idea being there would be hard to make these successful in the marketplace. In addition, the flexibility or I should say the innovation was also reflected in some of the structure of the statute itself, and in particular I will talk about it here in a few minutes the contact that substances may be generally recognize and had safe and therefore not be subject to the premarket approval of regime of statute, and that's the concept that remains very active and lively today as all of you work in this field know, and I think it has big implications for Nano technology. The basic idea behind the sunset of course was the substances are new uses of substances that had been fully tested, the information about safety had been in the public domain, and there had been general recognition among scientists and documented (indiscernible) recognition among scientist that is the safety of the materials demonstrated in those substances would be considered under the law generally recognized as safe and exempted from the food definition in the law and by virtue of that exempted from the environment of premarket approval, and again this was intended to avoid having what is a very formal rule making process to which (indiscernible) food additives having that be required every time there is something new in the food supply but in cases where the safety of that new use is clearly established scientifically and importantly in the law of established on the basis of the same quantity and quality of scientific evidence that FDA requires to approve substance as a food additive, so in addition to the flexibility and innovation of that concept it also had advantages for FDA because it kept FDA from having to use its resources to go through the formal approval process for every new use of technology, so with this background in mind, mind, I want to make two broad points that do frame into suggestions for the agency about steps it should be taking as the oversight of nanotechnology unfolds. The first is that the law, and its requirement that marketed try of new technology be based on scientific testing, I really think does put a burden on FDA to provide scientific leadership in arriving at conclusions about what testing is adequate, what are the methodologies necessary for companies to successfully (indiscernible) their burden of proving materials are safe. I will talk about that point a little bit more in a minute. The second broad point I want to make had to do with the GRAS concept itself and its implementation. I really do think it is incumbent on FDA given the history of the GRAS concept, given the fact that there are many substances that currently are approved by FDA food additives or listed in the food contact notification list is as having gone through the (indiscernible) process all some of these are substance that is are subject to being reduced to nanoscale, and the question is how does the graph (indiscernible) scale material apply to the nanoscale version, and I want to talk about it or at least give my views that subject as well. So with respect to the issue of scientific leadership and resolving the issue of what are the appropriate scientific methods, I mean this is kind of an obvious point and I think from where I sit, but I do think that because the system is basically set up as putting a burden of proof to do the right testing on industry, to prove safety, FDA is seen as the as the of whether the standard for approval of additives or ensuring the safety for substances has been met, the FDA has to be not just a passive umpire but has to be an active leader in providing the guidance about what are the scientific methods that are going to be appropriate, and we're clearly in a mode where I think previous presentation made clear and anyone in this nanotech discussion I think it is very obvious we're in a state of scientific development and evolution to figure out what

are the right methods, and my suggestion essentially is that FDA needs to be out there providing the initiative to do this. It can't develop the method T doesn't do the testing, it doesn't -- it will never have the research budget to do a research required, in the sense of just how expensive and what a significant undertaking this research is, but I do see a role for FDA in the actively engaged with the scientific community, with the industry, in seeing to it that we arrive sooner rather than later at accepted validated methods for evaluating the safety of animal materials and effectively exposure and toxicity testing elements that far safety evaluation. This obviously requires commitment of management, time and resources, and I am the first to acknowledge that FDA doesn't have those resources, has not been given those resources, and I think that it is incumbent on the Congress and administration to see to it FDA does get in this work, but if you share either the safety objective overall or the innovation objective or presumably both, I think you have a real stake in seeing to it that FDA (indiscernible) scientific leadership. Enough on that. Let me shift to the more purely regulatory policy point I want to make.

That has to do with the premarket approval issue and really the issue of giving clarity about what's the regulatory pathway today for food related applications of nanotechnology, and again I think it has arrived in the multiple context that I admit some of them. There is of course the question of how the rad concept applies, given the state of science today, is it possible for a particular application of nanotech, particular food related application to be generally recognized as safe under the legal standard of GRAS stated today and second related question, given the food regulation I mentioned, how do nanoscale -- how do those regulations apply to nanoscale versions of already regulated, already approved food additives, and likewise in the context of notification same question can be asked. These all -- these questions all have to do with what the premarket approval principle and food additive amendments in 1958 needs today in the context of this technology. I think it is an incredibly important question as FDA to stand the public skiings aching about the production to the food supply, and it is I think it is important to FDA's credibility it is able to be clear about what the meeting of premarket approval that principle is today in the context of nanotechnology. My advice to FDA is sooner rather than later it provides guidance on that point. I think from my vantage point, and I speak as a none stop sign Tiss who listens to scientists scientists carefully to try to understand what they're saying, but from my vaunteddage point what this really boils down to is acknowledging that a nanoscale particle that has new properties, novel properties, distinct from those associated with conventional scale properties, substances, should be deemed a new substance for purposes of safety evaluation and for purposes of application of regulatory scheme. It has new properties. It is different for purposes -- the very purpose for which we do state evaluation in the first place know whether the particular properties and substance know how it interacts with biological systems and scientific data driven basis for knowing that exposure is safe, and so it is very difficult from a lay perspective and regulatory policy perspective to see how a substance with novel properties that should not be considered a new substance for safety evaluation purposes, and that would mean, again, that the approvals, the existing to that relations, for example, would not apply to nanoscale versions of the material, and it is pretty clear in the FDA regulations and policies applied historically that if in fact the properties of this new nanoscale material were not addressed in the safety testing that was the basis for the original food

additive approval of conventional scale material that that novel material that, new material would in fact require food additive petition, but I think there needs to be clarity on that from a public standpoint standpoint.

The same conclusion would probably be expect the (indiscernible) GRAS state. When there is a degree of (indiscernible) science about how to measure exposure, for example, dealing with the issue that was raised just, for example, do we know really what is the form of the substance when it is actually in the human system, as opposed to the form it might have been when it was in the media views and toxicity tests, when we have basic method questions, it is difficult for me to envision how a substance can achieve generally safe status. We need validated methods, I think, before we can entertain GRAS date for nanomaterial. We need much more testing information in the public literature, and we need statutory cry tear a for GRSA states and general recognition, common knowledge in the scientific community of relevance for community that that use is safe. Now, the reason I think why I raise the issues is that at this point, this early point in the development of nanotechnology, I think it is critically important that the agency be able to articulate clearly to the public and industry what is the regulatory pathway today for nanomaterials, and one thing I would emphasize, I think I know it or at least I hope I would emphasize what it says today about regulatory pathway isn't necessarily what would be the regulatory pathway five years from now and ten years from now. In the GRAS state, it is a tool of flexibility. It is grounded, though, in the state of science, and as science evolves, from my vantage point the possibility could well develop that nanoscale materials would be eligible to GRAS status, elevated to the process, but my point is on the science today as least as I understand it, I am completely open to being persuaded I am totally wrong on the science, because my knowledge is entirely derivative of what I hear scientists say, but given my understanding seems to me we have to be clear today about what the pathway is and right now (indiscernible) approval principle seems to me should be the one that ought to be seen to govern. I think the strength of the premarket approval system, this is my last point, is that by shifting the burden of proof to the agents or industry by requiring testing that meets FDA standards that, whole regulatory regime has the power to drive the development of science, to ensure that the work is done that will create a scientifically sound basis for assuring substances, so my closing advice is to let the law created 50 years ago drive the generation of knowledge and the understanding that will commit us to ensure long-term future of the safety of nanomaterials. I will stop there. [APPLAUSE]

Thank you. Questions from the panel?

So supposing that new properties would cause something to be viewed for regulatory purposes additive, I think paraphrase what you said, why would you limit it to new properties, materials of new properties that are also nanotechnologies?

I don't know the proper nanotechnology. I think it is the property that is count. I guess my point is that it is hard to but an arbitrary number on the size of the particle that drives (indiscernible) the way I see it the answer to what is the right way for pathway eligible for GRAS as the propers, change in property that is change the way the substance potentially

behaves in human system, that creates the novelty that makes it a new substance (indiscernible) and safe evaluation purposes.

And you see easier task to defining new property to essentially defining nanotechnology products?

I made no representations of the easiness. I think, though, that I have harder time sort of understanding the value of struggling over side definition. I don't know what the difference for evaluation purposes between a 90-nanometer and 110-nanometer (indiscernible). I think you get scientific consensus that it is a meaningful dividing line and from the purposes of the safety evaluation. I think what FDA's difficult task is to provide the guidance, layout cry tear a for judging whether the properties are different in a way that makes the nanoscale version or any other modified version particle size or whatever version of regulated substance or substance that may have been grabbed conventional scale to layer the cry tear a that draws the line between the conventional material and one being used for regulatory and safety evaluation purposes.

One more question. I think implied within the constructed is the Poe potential or at least the known nature to (indiscernible) properties so manufacturer would either intend to or know about the new property and somewhat convey (indiscernible) to have the intention although component?

The whole regulatory use is based on intended uses, and I think there is actually -- the law as it is written is not intention ALITY per se as you're using the term, judging whether a substance is (indiscernible) food additive review or not based on the manufacturers intentional of property change but it is hard to imagine there is not high awareness and purposefulness in reducing particles to nanoscale to achieve the functions that is make it work in the cost of doing that, so I don't see that as particularly an issue, and I don't think many companies are responsible for proving safety as a material under its intended conditions of use, and that includes whatever properties it has, the responsibility of the company whether intended or not.

Any other questions? I would like to thank the speakers again. We actually ended up a little early. [APPLAUSE

Pardon?

12:30. Have you seen the schedule?

(laughter).

Lunch isn't on the schedule.

It is on my schedule. It will be worked out.

(laughter).

Yeah.

Believe me, I never miss lunch. Okay. You have heard presentations from our invited speakers, their areas of concern, various areas we discussed this morning of nanoscale materials used in food and food packaging and also dietary supplements which are of course food. Now it is time to hear from people and organizations that have requested time to speak at the breakout session. Again, I will give a two-minute warning when appropriate, so please keep your comments brief and to the point, and remember you can submit the more detailed comments to the docket. Our first speaker on the schedule is police station Robin Gay of Robin Gay consulting, and she is -- she is ready?

(indiscernible).

You need the controller?

Yeah, that would be great.

Keep the microphone close so the transcribers can hear you.

They're having a real problem.

I am Robin Gay. I am a (inaudible) and also the President of the roundtable technology consultant, so a lot of these comments also incorporated comments that (indiscernible) submitted. I am going to be talking about harmonization and also talking about nano and consideration, stability assessments and self nano. (indiscernible).

Harmonization, these will be worldwide regulatory reactions to nanomaterial, and really prudent for the agency to develop, validate and harmonize specific aspects of toxicology testing, and that would avoid unnecessary retesting if you want to submit those countries or agencies, especially if you're going to be working with animals, doing studies with animals. Due to the number of potential uses and innovative nature of nanoscience, approaches to the safety nanomaterials and products containing nanomaterials should be taken on a case by case basis. We have seen many people already this morning talk about case by case basis. I think it is really important. However, we should not be too restrictive, as nanomaterials appear to offer valuable advances that may not be completedly appreciated or understood at this time. There are a lot of things when you go from regular size down to the nanoas we heard that there is some changes and really don't know what those are until we look for them.

I want to talk about nanotypes, and the (indiscernible) community and nano industry are becoming increasingly aware of literature and presentations of a scientific nature that present safety concerns for nanomaterial but don't really fall under rehabilitated methods or results the FDA is looking for, don't really follow TLT qualities and FDA does (indiscernible) or in the guidance or regulation of nanomaterial. It is just should be based business as usual for the FDA, then, and science should not be ignored, but used as a tool

to help develop initial testing for (indiscernible) studies and products. Guidance needs to be developed according to fiscally sound (indiscernible) and well documented.

For some considerations we already had talked about the increase in surface area and increase in particle size, and that could change the characterization of products, so there is strong need from the red book, FDA has saved nanomaterials submitted, so we do need guidance from the FDA as to what to do, so other considerations for red book would be (indiscernible) ex pregnancy, conduct -- ex suppression, clinical studies, more EMEA studies, specifically distribution, and ADI currently expressed as map and might need to think about how ADIs are reported, cumulative human exposure, and safety factors, and these could be added to the emerging issues section so it doesn't interfere with the conventional (indiscernible).

So more red book considerations would be based on nanomaterial handling and storage for safety testing, need to look at that and define that for safety investment protocols and reports, and that would be vehicle, materials are in different vehicles, we could see different effects, different tax logic effects, (indiscernible) are used is important, too. The material (indiscernible) to a container, for example, shipping methods and conditions also needs to be addressed and other potential considerations. These would really be on a case by case basis. Every product would be different different.

Where extensive stability testing needs to be done for nanomaterials because they do have clinical particle and surface properties related to the mechanism of action, biodistribution, and also pharmaco kin net I cans, and nanomaterials has been known to change particular properties and storage and (indiscernible) condition and we were just talking about the FDA agency should consider that because one of my clients (indiscernible) nanomaterial seen based on different storage conditions, and after awhile looking at stability that the product does change.

Can you speak closer to the microphone, please.

Yes. The stability assessment. There should be more focus on stability assessments which is due at the same frequency probably as ICH recommends and validate or justify the relevance of elevated storage temperatures and utility in making stability product 40 degrees, storage conditions may or may not be appropriate for some nanomaterials. There is need to add to traditional (indiscernible) analysis including analysis to things like potential for holding aggregate, particle size, particle shape, surface chemistry including (indiscernible) potential, surface area determination, DEM or SEM also would be important to look at.

Also, I want to address self nano. When I was at the ISSC meeting I was talking to somebody, one of the speakers actually, and he was saying a lot of companies in the food industry don't really come out and say that they're using nanomaterials. There is a lot of apprehension of people consuming nanomaterials, and companies don't want to take -- don't want to take a level comparable to like genetically modified orer radiated foods, so definition of nanoshould take into consideration path logic and safety parameters and not

just size for example if you have a molecule that's 250-nanometers, if that does change the characteristics of the material by reducing it so that (indiscernible) size that should be looked at too, so definition of nanomaterials should not just include something under 100-nanometers which it will be characteristic of.

Property safety testing and publication would help dispel concerns as well as increase the public database on nano safety, and that would make people more or companies more forth coming in saying they've got nanomaterials. All right. That's it. Thank you.

Thank you.

(applause).

Any questions from the panel?

Actually I have a comment. Sorry. We actually eliminated the emerging issues of the section of the red book, so, however, we may bring it back, and are you recommending that we spell out everything?

I don't think -- I think everything has to be addressed on a case by case basis.

Right.

There are so many different aspects and so many different --

Because we've noted here that it would be very difficult.

It would be.

And testing you're recommending, small companies, it could be financially prohibitive for them.

Yeah, I think it already is for some companies.

Yeah. That's where we're going, so we need to have strike a happy medium on how we start looking at these materials. This meet willing hopefully will give us that type of information. Thank you.

Another question?

I guess I am not sure I completely followed your considerations. Are you suggesting that we need a different exposure paradigm, different than the issues with basic?

I think it would be -- it would really be based on the characteristics that you see when you're testing it, when you're testing the product. Are you talking about (indiscernible) levels and the different studies done and the different concern level.

And your comment about mass.

Okay. Yeah. Because the nanomaterials might be better expressed based on particle size or surface area or number of particles, and I think until we learn more, I think we really need to try to figure out how we're going to express it, if we're going to keep it as a mass basis, then I think we still have to take into consideration the particle size and surface area so that might have to change the surface area or at least take it into consideration. I don't have the definite answer for that. I would definitely say to keep the surface area particle size, number of particles under consideration, and you might have to do some changing. There might have to be some changing.

Thank you very much. All right. We'll have one more speaker before lunch for those whose stomachs are starting to growl.

(indiscernible) Boston Mass.

Good morning.

I think.

Having a little trouble with my voice, so fortunately many of the points I had planned to make have been made by previous people, so this will be very brief. I want to emphasize simply three points, but it is my view that existing framework for testing risks and establishing safety are going to need to be updated to address nanospecific aspects of materials, and there is currently great deal of concern and uncertainty about these risks and that level of concern that's been expressed both technically as well as socially really is going to warrant a broad evaluation that looks at the life cycle of these -- adopts a life sickle view and also broughter and public and societal issues. Many of these points have been covered already. Existing frameworks are going to have to be amend to do consider different units of measure it. For example, how do you integrate nanomaterials for existing substances under accumulated exposure framework or develop ADIs when mass is clearly not the appropriate measure.

This is going to require a lot of integration and collaboration, and ex terrible as well as internal communications -- external and internal communications within FDA in order to develop the policies to ensure that exposure results in -- toxicology testing are integrated.

There is concern as we heard that the responses to adopt a case by case approach, and that's appropriate given that there is no overarching widely accepted framework. However, that may not be transparent enough to satisfy some of the public concerns. The success of proactive -- proactive approach to increase confidence, so an approach that is (indiscernible) life cycle risk issues generally and also specifically for nanoscale materials considering, for example, when in the product life cycle is exposure likely to occur to the particle, many stages of the life cycle where there would be exposure, but,

for example, a categorical conclusion of the environmental assessment would dismiss those broader environmental concerns.

Also because risk is a social construct (indiscernible) address the issues that are going to affect public trust and confidence, so good science is obviously important and requires a positive perception is also important. It is important to align the research with an analytical framework. In other words, to know what your end point is going in so that as the message is developed and as the data is developed, it can be brought out in a conceptual framework, and address what is nano about doing risk assessments for engineered nanoscale materials. The risk assessment toolbox offers a number of options for making this management decision under certainty, and there are some tools available to conduct screening analysis for example to ascertain whether there are specific attributes of a material that are going to warrant a different testing framework. I want to take this opportunity to mention that this already awhile ago that later this week we will be discussing issues of how the risk analysis framework needs to be updated, what it -- how it can reform nanomaterial risk assessments at George Washington University as this is a public workshop, and will be delivering the issue and if you're interested I have a few slides with me or you can go to SRA.org. In terms of considering life cycle approaches, this provides framework to consider both the biological and environmental exposures in this one cohesive framework, and there are a number of proposed frameworks out there, and at this point nano (indiscernible) SRA proposed an environmental assessment is one proposed and under voaftion by U.S. EPA (indiscernible) office of research and development to be familiar with the nano risk framework. I did for more broadly considering how to assess the risks of nanomaterials. Finally, it is important for FDA to provide guidance and public communication such as this and more broader public communication because in the absence, the approaches are likely to be developed, and in that case, it will be different methods used by different industries to (indiscernible) the if ca of the product and need for coherence as (indiscernible) and in addition the issues of perception are going to need to be addressed so any message includes transparency and responsiveness to concerns that might not be addressed (indiscernible) client.

So a life cycle approach warrants the use of higher requirements for nanoscale materials and until the uncertainties are understood and boundaries of this science, of this diversity of impacts that occur can be characterized that includes very public review process, and participation in development of the testing requirements to ensure they're acceptable. And the need for interdisciplinary research and it is determining how to think about the life cycle and also to be very transparent and properly engage the public.

Thank you. Questions from the panel?

(applause).

Dr. Canady -- okay.

I hear your talk on (indiscernible) discuss environmental aspects of FDA to review and of course FDA has numerous responsibilities (indiscernible) applications. I am wondering --

I wanted to ask you do you think there are greater concerns in that area in the area of food or other areas? In a way I want to ask you why are we so lucky to have you in this session because one of the other four?

(Laughter).

I think one of the reasons that it is important to consider environmental aspects of food and (indiscernible) containing materials is the wide nature of disbursal and may not be a way to characterize it differently from drugs certainly is a way to characterize it differently than (indiscernible) which should have a more limited use, I would think, and consumer items approval for. Those are all -- the reason I am here is I do believe it is widely distributed globally, in fact, and raises a lot of concerns, whether they're used, where they're disposed of.

(inaudible).

I will pass. Thank you.

Other question from the panel? If not, we get to go to lunch a few minutes early. We will resume at 1:30. Try to be hereby 1:15 so we can get organized and started on time, and we will resume when the rest of the speakers that have signed up to speak. Thank you, folks. [the conference is breaking for lunch and will resume at 1: 1:30 p.m. Eastern Time]]

Please take your seats so we can get started again. Welcome come back, folks. I hope an enjoyable lunch. We are going to get started. I have to correct one minor oversight in introducing the panel. I went back a year and a half before Elizabeth of marriage. This is Dr. Elizabeth Sanchez. All right. Our third invited speaker that has signed up to give a presentation is Mr. Ian Illuminato. Come on up.

I am with Friends of the Earth. For those of you don't know we are an international organization. We have offices in 70 countries. Today I am going to go over some of our recent reports outlining some of the products we have on the market. Also I would to mention that we presented the comments at the last public meeting in 2006 then along with those comments we submitted further comments from the public, thousand of the comment. And other internal organizations as well. I believe the total is over 30,000, and these were basically that FDA knew something about products and technology currently on the market. It seems that these have not been regarded seriously. There are urgent concerns from consumers to at least be able to make a choice when it comes to their right to purchase products. In 2006 to visit of cosmetics and now we know that nanotechnology is even more intimate. It is now if into packaging. That intimacy is really something that we believe is an even more urgent call for regulation. In our report refund about 104 products ranging from agriculture coracles to process fruit packaging and food materials. Each of these is just a small portion of what is on the market. In service with companies we have found that there is some clarity on which companies had been using a nanotechnology and their products. So this, in our opinion, is just a small number. There

is a mechanism that shows between 150 and [Speaker Unclear - Audio Faint]. Other estimates have shown almost $6 million. So this is definitely a transformation that we are investing in heavily. Some of the major players of their are investing in research and development and already have [indiscernible] of the market. And these companies have the means to do so. This one is changing that [Speaker Unclear - Audio Faint]. So again we really stress upon [Speaker Unclear - Audio Faint]. And this is a quote which we think is a general forecast of what some corporations might think nanotechnology will print. Future generations of humanity will be affected the matter how rich, sugar, all the things we love will now have more restrictions on them in the future did all food will be [indiscernible]. Achieving goals will be change. If this were to happen [Speaker Unclear - Audio Faint]. It's something important in people's lives whether it be characteristics of a change in food consumption and what food will be. There is really at the Texas on the public information.

Could you step closer to the microphone please.

Some of the products we have found our children’s products. Those are the ones we are more concerned with. There is a nutritional supplements offered at whole Foods with iron in it. There is also various food counters materials we have also found food packaging and McDonald's and Cadbury chocolate wrapping. Also Miller's Draught is using a number of particles and some of their glass bottles. There is food additive; this is a company in Australia. Plan growth treatments and various chemicals, the ones on top markets are Frilomax on the marketplace by Syngenta. In our report we highlight some of the studies this is definitely -- there is utility of both ends. Here are some of the red flags that we can see from current studies. One of them is that nano particles can be more reactive. Nano particles can have greater actions in our bodies it can introduce [indiscernible]. We also don't know along the lines what different pathological effects could come out of nano particles. One of the biggest issuers are is a very few studies we have on exposure Tech nanotechnology periods as most of your note it is calculated by risk. This is a "is as you can probably count published literature on is budgeted nanoparticles on both hands. There is also in our mental risk. The environmental balance depends on the very symbiotic relationships. We have found that we can develop more harmful. This is considered to be poisoned. It becomes that lets more reactive. There are also studies showing that dioxide which can be in food processing can be toxic to algae which is important attrition for marine life. Nano [indiscernible] as well as being toxic. And nano hydra chemicals, even though they are more potent they can also be possibly more toxic. Our concern is that with food additives and various ingredients in food supplements should require authorization from the FDA. Many factors can legally market a product flow of the chemicals have already been approved for commercial use. It has already been approved for use in larger particles form. Nanoparticles does not require additional authorization despite the fact that they introduce new risk. We also think that you should distinguish between a substantive or nano particles so Some of the guess we see or other products, the packaging is not really regulated. It has no reason -- node migration can [indiscernible]. That can be extremely risky. Also see a bit of contrast in terms of and understanding that nanoparticles are very different. When it comes to labeling and regulation we are very much of its stance that because there are some special

properties. This doesn't support a finding of materials present for safety concerns. So we think that a lot of these contrasts should be mitigated and that there needs to be a lot more parity. So our position is calling for [Speaker Unclear - Audio Faint] for all products that contain nanoparticles Intel there are specific safety laws established and the public has really been involved in thinking about and that agencies are vetting what the public really wants. If other recommendations, they must be extended. Transparency is needed for the assessments. Again, public involvement and the decision making in support for distinguishing is also needed because we have found that nanotechnology is something quite phenomenal, but at the same time some of what industry is working to use metal particles for such as industrial agriculture some might think are outdated ideas and terms of how new systems should be considering a monoculture. There are very large farms ticking away from small-scale farmers the wrath of world. We know that farming is an important industry for many small fields. That leaves have of the world's population. So and thinking about no technology and agriculture we really have to be looking at that big picture. And another point, with that bigger picture thinking comes along the fact that nanotechnology comes from a quantum mechanics of physics. That is a very new and exciting way to think about science and is a science that is really breaking the barriers and making the impossible possible. For example, and quantum physics you could have one particle into places at once which is really mind blowing. That is a powerful new way of thinking what humans are capable of. When we think about nanotechnology specifically and products I would specifically remind the agency that this is just a small part of a very new a setting way to think about our lives and our potential. And also not forget the Royal Society's recommendation from 2004. They recommend that ingredients in the form undergo a full safety assessment such as a relevant scientific body would conclude. We recommend that manufacturers publish details of the methodology before assessing the products containing an of particles to demonstrate how they take into account the properties of nana particles. They also recommend that the ingredients should identify the fact that manufactured nanoparticles material has been added. If anybody would like to have a copy of my report simply contact me.

Thank you.Any questions from the panel?

You recommend that the FDA considered labeling of everything.

Engineer in and of particular.

That is what I'm getting too. How would you provide a definition on the one extreme excluding labeling as having some particle and did that has to be in that has killed range with that .001%. The blood to be very specific about properties so that you only label of few things. How do you help us bridge that wide with you might have in terms of considering labeling.

Well, companies are using an of particles because of the various properties they own. They enhance their products. In that case if a company is -- has the intention to use metal particles to change their product in some way and offer something different that should be identified to the consumer. There are countries in Asia and specifically in South Korea

for example. The public is really keen on nanotechnology. Some of the Cassies are actually lying about the use of nanoparticles in their products to give them more value. So this can work both ways. In a country where we talk so much about freedom consider freedom definitely an important part of that.

Other questions? Thank you very much.

Our next speaker is Dr. Betty Blue so, Research Scientist.

[Speaker Unclear - Audio Faint]. I am a scientist with the institute. So I would like to commend the FDA for preparing and inviting us to speak at this public meeting. I will tell you a that a bit about what I do. We are a scientific non-profit society. We also work and professions closely related to food.

Could you move closer to the mic please.

Yes.

You could pick it up.

Okay. We have 22,000 members from all over the world. They work in the area of food science and technology and are all from industry, government. Our vision is to provide food supply can to reach into health care of people which I think is in support of the FDA mission. So I asked you [Speaker Unclear - Audio Faint]. In the year 2000I established but then initiative which is fed by our now science advisers. Those are from government. We started an initiative in partnership with the North American branch of the International Life Science institute that is in North America. And that nanotechnology the lab is a part of the National Cancer Institute to kind of go through some establishing comprehensive refused on the complications of no materials and food. Then the skills science and technology. If their goal of this initiative is to kind of established the State of the science and applications and implication of than a science and also to identify key data. And this we hope we develop a comprehensive report to stakeholders and to develop [Speaker Unclear - Audio Faint] in the issues. So we commend the FDA for being supportive of this initiative. We ask that if we continue to support the initiative we come up with that information with the issues we are discussing. I would like to set that we strongly encourage the FDA to continue to support and enhance collaboration efforts. The agencies including those who are at the edge and national level and those in the industry trend to develop the data that we need to inform. We also ask the FDA to promote and informed information exchange such that would help to further understand this new technology and have informed the position. Finally we ask FDA two [indiscernible]. We commend FDA for the support they have for the Standing research and has been to continue to do so so that everything they implement will be better. So that is what I have. I will entertain any questions.

Thank you.Questions from the panel? All right. Thank you very much. Okay. Our next speaker is Dr. Michael Hansen, Senior Scientist, Consumer Union.

Thank you. I don't have any slides. [Speaker Unclear - Audio Faint] I would like to add that the FDA for this over Tennessee Tech comments on this session, this break out session on basically directing food and color additives. The basic position is that we urge the FDA to recognize that's a minuscule particles do exhibits properties and are behavior's and contrary to larger components that raises unique facility concerns so that separate safety assessments must be required before it sets particles or material may be used.

Could you step closer to the micro or pick it up.

Could be used for any purpose at be it's an ingredient or food packaging. So to answer in a certain sense your first question of what you can identify certain clauses of the ingredients are packaging plan is to arrive. You would identify as raising or not raising unique safety concerns and wine. In general a response to this question was on [Speaker Unclear - Audio Faint]. Those are defined as a mixture that is purposely manipulated as nanoscale and exhibit properties as a result. Ops all sides engineered material for food and color additives including contacts substances should require a full food additive petition he even if the macros kill version of the substances question was previously granted a petition work contact notification. In other words it does have the potential for structured dependent health effects which we're uniquely different than their larger component and the Texas the question. So in this regard we also agree with the conclusions of the July 2004 court of the U.K.'s Royal Society which concluded we believe that chemicals in the form of Net particles should be treated separately to those produced in large reform given the evidence that increased surface area can lead to greater toxicity per unit mass regulating the exposure on a mass basis to an end of particles and tools may not be appropriate. And that is just as we have to recognize that as particles could smaller and smaller surface area increases exponentially. So to take a single example let's take the example of 100 grams of lead. If you make that into a single particle that will be as fair that is 2.6 centimeters in diameter. Its total square surface area is 0.0002 meters square. If you take that particle size that 2.6 centimeters in diameter and reduce it down to 50 nanometers and then 1 00 grams, that would give you a total surface area now of 1,000 square meters. So that means you have increased 500,000 fold the magnitude, the total surface area since we know that this gridders surface area means greater reactivity with biological and chemical materials, increased reactivity with the immune system and we have seen data from earlier this morning showing that the same quantity if it is an smaller particles size can greatly increase toxicity. We also know from air pollution that small or alter fine particles are going to be known as size. They typically have greater surface area and are more toxic than larger particles. They can penetrate much smaller. Given the characteristic and the fact that some small metal particles are so small that they can evade the immune system or pass through the blood brain barrier or directly entering the cells and across cell membranes and even said nuclei since they can go to places that the other particles cannot for all of these reasons the FDA has to consider this to be new material with unfamiliar properties or a significant new use of material. That means existing food additive positions, food contact notification of or these craft determinations from microscope materials should not be considered valid for

versions made with the known as gilts. Either way a separate food or color additive petition must be required. At this point I would agree with Michael Taylor earlier this morning who basically said given all the unknowns we have with potential toxicology of these materials even how to measure them, even have to get accurate data on the migration, these things cannot be granted at this moment. Now, we know that for food content substances the so-called indirect food additives, those food contact assessed that they have a streamlined pathway through approval. The so-called food context edification is in place for the food additive petition. However the FDA can bypass this if it determines that submission and review of a food additive position is necessary to provide adequate assurance of safety. We believe that the FDA should state that due to the potential toxicology issues raised by business still materials and whether to use this food contact basically due to the exponentially increased surface area to of mass ratio and greater surface reactivity we think that food contrast of substances as a class should be ineligible for the food contact notification process and that a food additive petition has to be required. We also notice that for food contact substances in terms of doing an environmental impact analysis the FDA regulations can exempt components of packaging materials from the requirement of that environmental assessment under three conditions. That is one other that the substance is present in a Finnish food packaging material much greater than 5 percent by weight and is expected to remain within the fast-food packaging material throughout is used by consumers. Or if there is a component of a coating of a finished food packaging material work if it is a component of another food contact substance intended for repeated use. Those are all categorical exceptions south although it should be pointed out that the FDA does half -- does retain statutory authority to require any aid for any agency action that would normally be categorically excluded if the available data indicates extraordinary circumstances that would make the exclusion unwarranted and if there is a impending facts on the environment. The Consumer Union believes that these men and materials is in direct and indirect food and color additives creating such an extraordinary circumstance that would negate the categorical exclusion. And so the FDA should require full impact assessments and the ideal vehicle full environmental assessments and did do the environmental impact statements for all the uses regardless of whether it is a categorical exclusion. And for example I just pointed out that one of the categorical exclusions, if it is left them 5% rate. Again, that might not be appropriate because as I said the same quantity or mass of something when it is sustained and skill can be of heightened Texas city. So the general mass characteristics should not apply. However, there is one class of food packaging substances that we are particularly concerned with. Those are one where the food content substances are being used for microbial purposes. A bridge example is the use of silver in and out particles were several ions. Given that we know the FDA does require food additive positions for such food context substances if there is greater exposure than 200 parts per billion for that's substance again given the surrounding for potential toxicology of these materials we believe the FDA should require a full food additive position for any engineered no material and food content that has a bias title active regardless of the exposure level. As so rather than use the 200 parts per billion as a cut of at this point there should not be a cop. It should be of required. Furthermore for the environmental assessment since we know that none of silver is being used for microbial purposes in many different products and have been at least tumors 60 such consumer products that were measured in a

petition that was sent to the EPA that was signed on to by Consumers Union just last Tirpitz. These included silver and things such as food containers, slippers, source, bandages, a dietary supplements, other materials as well. So a consumer products said it is part of any in our assessment. The FDA should require the human exposure to lead and silver from all sources and all products should be looked at together and collectively rather than separately so that we can get an idea overall exposure. So don't just look at it because it is in one food content substance. We should be looking at all exposures collectively before the fruit attitude but-And it should be granted. Since we now by they regulate such products as pesticides when that purpose is being stated we think that the FDA should coordinate any such analysis with the EPA. We also think that the environment's impact should not just be a human impact, but for all of this. That should be considered for human exposure, but for the entire mental exposure. That means a full life cycle analysis should be used. We also think that when you are doing such a full life cycle analysis the FDA should work in coordination with other agencies such as the EPA or Russia. And since -- I will end very quickly. These are materials that are of the greatest concern. I think to characteristics is the fact that these are minuscule particles, that is the fact that they have a very small size and therefore a huge service area might be more reactive and the fact that they could be migrating from packages into food given that there is potential increase toxicity per unit mass, we have already said that some of the threshold for toxicity testing should all be requested. So whenever you see a limit for a new Texas City tests the guidance care is a dietary concentration for toxicity testing for food context substances given the uncertainties we feel that number is not small enough. So until we know more rethink that the FDA should require full food additives petition for any use of these materials and food context absences' regard to the exposure level. There is also potentially greater surface area mean greater availability. This could mean a greater toxicity. Pleistocene, there is a company out there called new trolleys which has a related technology which they call a no vehicle. The updated the claim they are for fighting. They can deliver up to three times the amount in the bloodstream compared to eating such to me desk. We notice that there is [indiscernible] containing something that was recently approved by the FDA. Like the team, it's unclear to us if it there will be harmful effects from an upper limit. So the purchases would need to be determined because if you encapsulate things to a bioavailability substances which might be considered safe might actually include [indiscernible]. So it could be toxic. That should be looked at. And again with this color additive petition there was about any mention as to whether the fortifying vehicles could be used for that color additive petition. We hope the answer to that is no. Finally as for the seventh question, how can they better regulate issues and packaging components, the rise for an attack and public industry, again I agree with Michael Taylor. I think the FDA needs to send a very clear signal to the industry of what exactly we need going forward. For us we believe that should be to attain quality acceptance. The FDA announced that it will consider all engineered materials that constitutes a novel materials and therefore must undergo a full food or color additive petition before being teamed as either a direct or indirect food additive. So that tells the industry that these things will be considered, that this either through your color added to his or her food notifications are inadequate and that all those products have to go through. That would be that the line. Then also we think this should be an announcement for requiring of labeling for all products that contain these engineered materials. This is

because they have different properties and because it would constitute a mutual fact that should be exposed.Thank you.

Thank you.Questions from the panel?

Thank you.A couple things.When he said about that labeling. My question is what type of leveling do you propose, something as an ingredient label? I guess it depends what it is. First I think anything that is an engineered than unskilled material should be treated as opposed to as the devil's stuff. In terms of the kind of labeling, that should be open for discussion. If it is going to be -- if these things are considered food or color additives or indirect additives then they can required to be labels. I don't think you necessarily needed as a warning label, but it is to be clear if you are allowing this as a food or color additive it should be required to be labeled.

Thank you.The second question I had this you mentioned the use of food context's substances and in particular [Speaker Unclear - Audio Faint]. Are you aware of any published study that has demonstrated a particle food context of sense will reach or become more present?

I don't.That is in part because there are basic methodological are rules for how you go about doing that. Member to there are issues as to how some of these particles, how they might behave differently. So that means if you would do a safety test on silver and lead added the size and characteristics may change. Those basics are you can make sure you're doing the right testing because to have something migrate from a package into the food, it's going through different microenvironments. Sens particles can change there are some basic questions we would have to answer before we can even get to your question. I would turn that around and say I don't know we've been mistreated this was a problem. But until we have data that can either say there is no evidence of Aiken turned round and said but in the struggle. So the absence of data should be concerning.

To you think that this program should not be used for any material? And just wondering what information you envision we get by the submission of a food and to petition?

This is just that the feared contact notification is a more streamlined system so I think a better would be more rigorous if we did it as a food additive petition. And I . out at this point we don't have anything to say that they are regarded as safe. That might change as we get a lot more data, but I do think that because the food additive petitions are a bit more rigorous than just the contact notification to drive the right be some disagreement over that, but it is considered more streamlined. Maybe some code should disagree. You have the same level of testing, but I think from a similar perspective if it looks like you're going through the more rigorous process that sends a strong personal than the more relaxed of the let which is how it is perceived and dart about. Did but.

I will give you another chance at that. My question was going to be what you think we would get of of the petition process given that they are for the same set of recommendations. Correction, the level is about 100 times higher than the level where we

actually recommend toxicity testing. You suggested 50 parts per billion. The couple is actually have a part per billion. If you want that at something you may know what you ought to say. You want to ask something about what we must derive from petitions courses notifications given ahead of Digital to reduce . Okay. The problem might be with public appearance. Put it that way. Because it is talked about that food contact notification is talk the left and a streamlined path where. If it is scientifically just as rigorous that is fine, but since that is part about it that way it just seems to me that politically you have to go for what appears to be the more rigorous one. That makes it resolved to the public, even if the scientific rigor. If they truly have that I am fine. But says it has been talked about publicly they do talk about food contact has streamlined. Some people in the public might take that to mean less stringent. So given the unknowns I was a year on the side of appearance when the more rigorous even if it is the same level. He cares what you want to give -- the message you want to send, we realize this is an issue. We are taking it seriously.

Thank you very much, Dr. Hansen. Par next speaker is Mr. William Schulz, a project on emerging technologies.

Thank you very much for the opportunity to address the regulation of dietary supplements made using nanotechnology. A word about my and experience. I was the staffer on Capitol Hill with the dietary supplement which is the best as a reformer for regulating dietary supplement. Supplicant -- subsequently the policy was involved in some of the early decisions in implementing desk statute. Unfortunately this is something that is overlooked, but in this area it is critically important that we focus on it. I understand it proves to be a separate section, but it was folded into the section on food additives and color additives which is fine. But I think the agency often [Speaker Unclear - Audio Faint]. The regulation is admittedly minimal, but if I want to explain over the next 10 or so minutes in this area I think your focus is going to be absolutely critical. If we could get a check -- let's see. How do I -- a word about the historical facts. I think any money at the FDA is very well aware. The eight areas are a dietary supplements has been a significant challenge. At various times agency has braided into its only to be rebuffed by congress. The net result is they have minimal authority to regulate dietary supplements. The introduction of dietary supplements with nanoparticles, it's going to give the agency a challenge. I think there are two questions here. The market share of dietary supplements has skyrocketed since the enactment in 1994. There has been a dramatic increase. Now what we are doing is seeing the increase of dietary supplements. The project on emerging nanotechnology is focusing nanotechnology products. A list of the projects being identified. Today there are 44 dietary supplement products. That is 26 more than identify into dozens six. So we are at the beginning. It is rising quickly. It is always easier and my experience to write the rules and impose them at the beginning. The agency and Congress are going to be faced with hundreds of products for matters of companies. This is the reason to focus. These are couple of the examples that were identified. Just examples. This is a product that is used to support the system. The little arches that our version of this will be particularly effective. It could be anybody from healthy people to the people with other types of colorize solutions. The effective one is a vitamin C product. Here you religious have an ordinary vitamin. This is

a good claim. The third one is not just in the company name but product and. It is comprised of the most powerful banana engineered mechanical ability. But these are just three products. There are plenty of others. They are going to be plenty more. So the problem, which I think you have heard about -- they agency has relatively little information on the safety of diet Cherry supplements. We are to start new of food that has been a run for hundreds of years. And talking about price market with a three supplements. Some of it has been around for a long time, but many of them pretty I knew. Think about dietary supplements is the release of the line between food and drug. In some cases they really contain ingredients every bit as powerful as drugs which are rarely sold and used to be drugs. There might be some perfection -- protection and the fact that [Speaker Unclear - Audio Faint]. But now that may change. Just as the agency has little information on how they're used and dietary supplements. The result is, there is no reason why a basis for concluding that the industry is actually doing testing. The agency has no basis for concluding with these products say. Consumers are left. So the question is in terms of resources and regulatory authority are they equipped to meet the regulatory challenge? We don't think so. That is what it talks about. First of all the agency is listed in the Thursday. There is no free market approval authority outside yourself. If the product qualifies that FDA should not recommend that the company wait for it to review data before the prize goes out. Before a new product as of talk about an of Cubans their is a free market notification procedure. The company goes ahead regardless as low as FDA is notified. Even if the FDA finds out about the safety issue of law is pretty tough in terms of what it can do. In other areas the company must in this animal. I put up the example just to show how difficult. In 97 the FDA issued a proposed rule to manage and really set the level that would be allowed. It did that because they're had been a number of deaths reported. There was a large adverse reaction. He is no final action was taken. By 2002 the manufacturer reported 15,000, very large compelling evidence. In 2003 they bend dietary supplements. This is one that is not available in most cases. Particularly cases and desirable. So what could the FT 80 today without additional stress storage 30? That is why I need to come back to this provision of the law that says a new ingredient [indiscernible]. As I said if it is a new dietary inherent you have to give that notice. So what I would suggest as a first sub is to explore whether a dietary supplements may use nanotechnology. If the FDA concludes that they are then there is a 75 day notice requirement and it is announced initially by guidance followed by regulation. The regulation but absolutely required. I'm sure there is as is lawyers which in the saddle. The notice is not a system that is. The company has relied on this for its conclusion that the dietary supplement in the saddle. If they are satisfied with that information they can take this product of the market. Does not have to show the product is safe. It is enough to show information is enough to support. This may be an area that is really very promising. These are generally quite difficult. But this is going to be meaningless without adequate reserves. I think everyone knows dietary supplements have always been understaffed. [Speaker Unclear - Audio Faint] in recent years it has gotten much worse. I think it has suffered disproportionately. I think today the program really is barely alive, barely able to do the kind of work that is to be done. To act effectively in this area at --

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Could you speak closer to the microphone please.

What that?

Because the to the microphone.

Devote additional resources. I have three recommendations that I want to go over. The first one is increased regulatory authority. The FDA should consider Congress to provide regulatory authority in this area, not just supplement data using nanotechnology. The kind of authority that we believe should be considered product registration, safety standards, pre-market testing and assault. The agency in the end is going to need additional resources. It is going to needs to make that case. If this includes resources from scientific staff and regulatory staff, and research. And third cars takes time to act. We think there FDA should explore what it could do with its existing authority. It could allocate within the agency additional resources. We should allocate additional resources dedicated to dietary supplements. This identifies dietary supplements. And finally to a study dietary supplements. In terms of regulatory and nationhood the issues and guidance made with nanotechnology are in fact [Speaker Unclear - Audio Faint]. And the agency could also consider his use of regulations for debtors supplements made with nanotechnology. And then we have to have the willpower and allocate resources to it to regulatory action. In conclusion the FDA today has no effective regulatory presence with regard to dietary supplements, and that is --

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Please pardon the interruption. Your conference contains less than three participants at this time. If you would like to continue please press star one now with the conference will be terminated.

Studies identifying and regulating nanotechnology. In the long run we believe congressional action may be required. Thank you very much for holding this session.

Thank you.

Questions from the panel?

I don't know where to start.

Thank you very much for coming out and talking to us and expressing your of long experience with the dietary supplements. I think you might recommend back in '94 the kind of hogtied as a little bit when they laid the legal responsibility to prove anything that was put in here. It was not [indiscernible]. It was very effective. What I would say is Congress is a place of political beings and it still is. There is a perception that we don't do anything. Let's separate the political statements from reality. Where we do what we have and w ith what we have got. We pushed hard with that new program when we don't have substructure evidence of safety. In fact you mentioned the regulatory action. I think if you read the letter very carefully you will see the status of that project is part of the argument made that was able to convince most of the manufacturers to kill off the market. We also have a new good manufacturing practice regulation which was required to have been adopted within two years of the passes of that. And because of those hefty a lawyer's you

referred to and others that took 12 years to get approved. So generating a new regulation or a new guidance is not all that easy. That might give you an example. This is a long way around to ask you if there are any other avenues you can see far as developing a policy of nano ingredients that would not require us to get to a regulation direction.

That is why I think we start with the guidance. It can even be an announcement. The agency could announce call we have looked at this. We have studied this. We have determined that products and dietary supplements made using nano technologies are nude -- new ingredients and therefore it is triggered. You don't need regulation. A regulation won't help the industry. I have to say I was in charge of FDA regulations for four years. I know how hard it is, but I also know that it can be done in a reasonable amount of time. I don't think you need to start with the regulation. I think you need to start with an announcement or guidance.

Guidance sometimes takes the same process to get through.

This is something that's is support from the top of the agency. It is to be made a priority.

I'm going to try to do this. I think is kind of interesting how you try to frame OR proposed regulatory framework for regular and dietary substances and supplements under the provisions of the new dietary ingredients. I guess where I'm going to start to go with this, what is central to the definition of a new dietary ingredients or what these dietary ingredients are. They are essentially substances that have not been previously marketed and that have been chemically altered. Now the phrase short-term chemically altered is not defined in stature to. So look for guidance on what chemically altered means the FDA has led to the Congressional record. And under that congressional test to indicate that chemically altered does not include the following physical modifications which will include minor components, dehydration, [Speaker Unclear - Audio Faint] or submersion of water. And it does where I am trying to to understand is under your proposal fell would nanotechnology or no particles fit under the definition of of being chemically altered? What might be the say a physical process of reducing something or actually encapsulating where there may not be any type of surveillance.

What were you reading from?

It is the Congressional record.

The interesting thing is that there is in agreement that was also in the Congressional record that there would be no history. So I think it is fine. It is important to read that, but you have to understand it does not even have whenever where traditional route was set of history would have because there is an agreement that the community reports which would not count as legislative history. So you've question is still exact right. I guess what I would say is Congress was not thinking about nanotechnology honestly in 1994. To the extent that nanotechnology affects the absorption of the products into the bloodstream I think you have got -- that takes you a certain distance to say that it has been chemically altered. At look, I am the first to announce. I tried to say all this very carefully. I don't

know the answer to your question. I refer to the agency to release the is and see if you can get there. You know, try and push it a little bit. I am just putting this up.

Any more questions? Thank you very much.

All right. The last speaker on the agenda is Ms. Jane Hulbert, D.C. its consultants.

I would like to think the FDA for allowing me to speak at this bridge gaps session. This is the only session that addresses color additives. My experience is specifically with cosmetic color additives. I think some of the points I would like to make -- as far as now the common use of the word in nanotechnology has been used to hype products for marketing purposes. It didn't come out of the scientific community. It came out of the larger community. Then the particles are not new. They have been used for years as long as I have been in industry. Safety has been addressed is directly under the FTA existing. They had been addressed several times in the course of published meetings. The first time was at a workshop back in '96 and inorganic and organic. That was in and out particles sunscreen. That was under the guidance of the FDA. As several people have mentioned to. Now we have the courage workshop. As far as the intended use of nanotechnology originally it was defined as the design of material at the comic or molecular level in order to achieve a novel properties be the electrical, physical, chemical, biological. Color additives, which is my field, these are not designed like it. So they really aren't data tech products. Although by the current definitions they are referred to as such. Of the color additives the ones I showed are the ones that have been reported.

Be available as nanotechnology ingredients. That is the certified name. As far as the primary particle size which is the smallest Kristol of the material that is created iron oxides are available and are very particle size between 20 and 300. That titanium's from at 10-250. Zinc oxide from 20-250. And this is actually 20-30 nanometers. This is the only one that was approved by FDA for cosmetic use. In fact these materials have always been this way. It is the control of the particle size down to the lower level that allows us to [indiscernible]. So materials have always been this way and always will be this way. As far as a distribution characterization and toxicology have been addressed at length by my colleagues who have presented at the cosmetic and track areas. I'd just have if you. Has your -- as your particle size distribution there is always a certain set that you have to make that may obscure the real issue. But everyone does what they can. You can back it up with either electron by guns or transition electron microns microscopy so that what you see, that is what one is actually talking about. If one does not see now particles they are there. If he sits and counts one concede there. That is what we've done. My colleague reported back in 2006. If these particles don't exist. They're aggregate such as 22100 nanometers. This is true for all particles. So on the case by case basis one has to judge. Why do we use them? Reason for their properties. The scattering of electrons flow of radiation. Particles are introduced and encapsulate. He have visible light from sediment. Therefore we get below 300 nanometers and are part of Sun's. We have particles of will become more of president to visit allied which is a novel property. That does not make them unique and engineered products. As far as the chemical properties 28 Nell with particles do not believe has molecules. The ability, density is the same as the larger

substances. As for biological and Ericsson's I can only speak for over-the-counter drugs. Even .02-micron particles do not penetrate. Theoretically it is into cellular and in the low has shown that these particles do not penetrate the skin. As far as what they do not take verses' conventional their work has been that the other chemical properties are unchanged the regulatory status is covered by the FDA authority.

Thank you. Any questions from the panel?

I got one. In the ads is needed clarification. Maybe I just a clarification. And the presentation he said that Micron particles would not pass through this again. Because work is no order soil. It has to be a huge particle to pass through the skin? Ten managers is much larger than .02 microns.

.02 microns is 20 nanometers.

Any other questions?

Thank you very much. Okay. Now we have vanished the speakers who have signed up. It is time for the open microphone. Maybe before we do that I would like to get some kind of indication of how many people are interested in taking inventors of the open by because we're at a point where we could take a break and come back but I don't want to do that if there are only a few people who want to talk. Special of hands could people indicate whether you're interested in using the open mike? I do not see any. I could be an auctioneer and auction off the time on the open mike, but if nobody is interested in using it we will adjourn the session. Thank you very much, everybody. We appreciate your participation.

[event concluded]