answer is, I don't know, because I don't think we know enough scientifically about what those safety toxicity issues are. I mean, Carol alluded to the biodistribution issue. Some of the immunological response issues I've alluded to before, and so again that's why my vote was no on the first question because I don't think we know what to say.

MS. MORRIS: Thanks. Well, one area that I don't think it's unique but it's certainly crucial is this size or physical characterization of these particles because I think that that is going to be important for toxicity, for biological activity, it is certainly important for distribution throughout the body and the need for a well characterized particle distribution, characterization of shape, size, aggregation, charge -- I didn't say that -- all of those certainly are important generally in formulation, but I think they're crucial when we're talking about nanotechnology because they will be so important in determining both biological properties and toxicity.

MR. MEYER: Again, I think we need to, if we can, figure out what we should be getting, what information we should know, and can we get that information by some means known to mankind? If so, and we're not getting it currently, then perhaps we need a guidance for it.

If we don't know, and I heard a couple of people say in different ways, they voted one way or the other because they didn't know what could be needed. Well, until we know what can be needed, that's not a reason to say, I don't think we should have a guidance, it's a reason to say, we shouldn't have a guidance now because we don't know what to put in it. So maybe someday we'll need a guidance, but in the meantime, if we could figure out what we need to know that we don't know, that we're not capturing with typical preclinical and clinical trials and everything else that goes into approval, then I think we can't do a guidance. So I would say one area that we haven't talked about much is stability, and some of these dosage forms are kind of complex and we need to look at the stability types of studies that are being done. It's not just simple chemical degradation. It may be particle size distribution changes or what have you that could have a big impact over time if we don't follow it once a product's approved.

One of my professors, Gerhard Levy used to say, the clay feet of bioavailability bioequivalence is we test one formulation, certainly with the generic drug, one lot, and we approve it. Now do we really know I there's something unique about that generic drug product that two years down the road sitting on a pharmacist's shelf, that drug product is no longer bioavailable.

So stability may be a key factor but in general to say what is needed, if we can figure out what we don't know, and we know how to get that information, then perhaps we need to prod the industry along with some guidance. If we don't know what to say, let's not say anything, much like I did the first time around.

MS. TWAY: Pat Tway. I can speak from experience from the first type, the simple type, the (off mike) example that was given by the second speaker, and you're right. You have to worry about particle size and particle size distribution and charge and all the rest of that but I think the tools are in place and I think the guidances are there. It's not different than a large molecule. You may have to do more stuff, you may have to use different techniques, but it's not that different. You have to be very careful of stability, but again the guidances are there. You can't do one lot, but you really have to watch it and watch it carefully.

I can't speak to the second type so I saw when I listened to this the simple molecules where you're just making them much smaller and then what I think of is more devices where you have the gold particles or the silver particles or the dendrites and thing I know absolutely nothing about and those may be very different and there may not be the guidances to do those, but I kind of agree with what a lot have said is I'm not sure we know the right questions or the right tools at this point to write it but I think they exist for the first type or for the simple type.

MR. MORRIS: Yes, this is Ken Morris. I wanted to add one thing to what you said, Pat, and that is that one of the things I think of from years ago when I talk about devices, of course there are diagnostic in plants and things like that, but I'm thinking more of the sort of science fiction view of this where people had talked about nanomachines that would be included in capsules, in permeable capsules that would then bore a hole, that's a ways down the road, maybe not as far as we think, but certainly the sort of thing that were it to come across FDA's desk, you'd want to have some background for, so certainly that sort of uniqueness, I think, is the kind of thing I was thinking more of although there are certainly others that I hadn't thought of that had been raised here.

So can we recap this? We need to come to a consensus on this. This isn't a voting question in the strict sense of the word. What I had in my notes in terms of the consensus is that the committee basically is focused on areas that are -- in terms of focusing on areas would be the uniqueness or those areas which are unique to the nanotechnology in question so that whether or not the guidance, the hypothetical guidance was more narrowly focused on a particular dosage form or route of administration, but the uniqueness of the nanotechnology should be the focus. The impact on safety should they be different than would be expected from the molecular entity by itself would be another area of the focus, that the environmental fate of such compounds and/or technologies, because again, not only might you be releasing the molecule into the environment, but maybe nanomachines someday, and that the areas that -- I'm sorry, the unique methodologies for characterization and stability and characterizing both the compound, the stability of the device, and the compound, as well as -- I missed one other point here -- as well as uniqueness that is related to the biodistribution.

Does that basically capture the consensus and then we can wordsmith this a little bit? Can we wordsmith this after the

fact or does it have to be right now?
So is there any -- does anybody want to comment or detract or shoot? Yeah, Art?
MR. KIBBE: Art Kibbe. I think this ties into the third question and the reason I said no is because I don't think we're ready for a guidance that's going to be helpful and useful. And I believe what Boswell said that unless there's absolutely a need for a law, there's absolutely a need not to have a law. So until we know exactly what we need to tell everybody about what they need to do, then we shouldn't start down that path. And the reason I say we go to question three is because it says, "What elements or factors should CDER consider to incorporate into the definition of nanotechnology?" And here differentiation between the first two speakers and their definition of what a nanotechnology product is, and we need to make sure that the agency understands or

articulates -- I think they understand, but articulates the difference between a device, which is a compilation of things put together in a very specific and controlled way, and the simple act of reducing particle size beyond micronized because we now have the technology to do that. And I think that is key to the way the agency looks at it and if I was recommending, I wouldn't put out a guidance. I would put out a recommendation to companies if they have a complex nanotechnology product that they're bringing along, that if they're not in here talking to us, they're in trouble. And if they're going the simple route, just go ahead and do it like a regular compound. And until the agency knows what specific things bridge that class, which is the complex system drug delivery, then we shouldn't have a guidance.

MR. MORRIS: So does what we said, though, in terms of the consensus sit okay? I agree with your point, but I mean because we're going to get to question three when we'll hopefully delineate some of those specific comments that you just made.

MR. KIBBE: I have no problems, I just don't think we need a guidance. I think we need a guidance on how we vote.

MR. MORRIS: Yes.

MR. KIBBE: But we don't need --

MR. MEYER: Marv Meyer. Ken, maybe we could vote yes or no that we agree with your consensus statement and that would be more official. I hate when it comes out in the minutes and the committee had a consensus, well what about the four people that thought it was a lousy idea? So personally I think you did a good job, but I'd like for it to go on record.

MR. MORRIS: Yes, everybody will get to see the draft minutes, so if that's what you're saying -- if there was anybody violently in opposition, but otherwise, as Art says, unless we really need to have a vote, we shouldn't. That's a paraphrase.

Okay, so at this point we're cleared to break for lunch, we're cleared for takeoff. We're number one for departure. And we'll reconvene at 1:30 at which we'll have the open public hearings talk. And then we'll take up question three in time to resume -- question three, then topic two at 2:00. Okay. Thank you. See you at 1:30.

(Whereupon, at 12:38 p.m., a luncheon recess was taken.)

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

(1:34 p.m.)

MR. MORRIS: Good afternoon, everybody, and welcome back. We're going to start the afternoon session with the open public hearing section. And do I have Connie's information? And so what we're going to do is we're going to come back after the open public hearing comment period to our question 3 on topic 1 as time allows if that's okay. But for now if we could we're going to turn our attention to lead in pharmaceutical products as the -- it's a general OPH, but the topic will be on lead in pharmaceuticals. Sorry, it's the Indiana in me.

So let me start by reading this statement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it's important to understand -- sorry, my glasses are old, too -- the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this Committee in consideration of the issues before them. That said, in many insurance and for many topics there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. And thank you for your cooperation.

How does she do that? So, can I introduce Dr. Weaver? No problem. No problem.

Our first speaker -- actually, it's the only speaker for this session -- is Connie Weaver. Professor Weaver is from Purdue University.

MS. WEAVER: Where do you want me?

MR. MORRIS: Right there if you could.

MS. WEAVER: Okay.

MR. MORRIS: Thank you.

MS. WEAVER: Great, thank you. So to honor your request, pretty much any calcium producing company or food company I've had some relationship with, either through grants, or advisory boards, or consulting, or something. The organization that I hope is planning to pay my travel here today is GlaxoSmithKline.

Let me tell you who I am and why I'm here then. So as Ken said, I'm head of the department and distinguished professor of foods and nutrition at Purdue University in West Lafayette, Indiana. And some possibly relevant positions I've held -- I was a member of the Institute of Medicine panel that determined calcium requirements that are still in existence for North America. I was a member of the 2005 Dietary Guidelines for Americans Committee. And I am a past member of the Food Chemical Codex Committee. My expertise is on calcium and mineral bioavailability, in general. And that's the area I would like to address -- is the special interaction between calcium and lead -- today.

So, today you're discussing lead limits. And I applaud your efforts to do that. I noticed in the advanced slides that you will be discussing factors that influence lead exposure and lead burden. So I want to call your attention to this special relationship -- this interaction between calcium and lead so that you don't throw the baby out with the bath water while you're considering lead limits. Because calcium and lead co-exist in nature, and if they're co-ingested, the calcium has a huge influence over the amount of lead that's absorbed and its risk then to the subjects.

So it would appear by looking at the slide on potential increases in blood level exposure that that particular interaction of calcium suppressing lead absorption is not factored into the potential increase in blood level increases. So, lead is a natural part of the environment. It exists in the soil and transfers into the food supply. It's a natural part of mind minerals.

Thus, food and other natural materials, including mind calcium carbonate will have measurable amounts of lead and possibly amounts that are in the range of those limits or those levels that you're considering today.

An important strategy backed by a lot of animal and human data to reduce the body burden of lead, especially for children, is to encourage adequate calcium intakes. Calcium competes with lead for absorption in the gut, and thereby reduces lead absorption in a dose-dependent manner. Dietary calcium has been shown to be inversely related to blood levels, lead levels, in about 3,000 black and white children in the NHANES survey. Higher calcium intakes have been shown to offset pregnancy-induced or lactation-induced increases in material blood levels. Thus, calcium supplements admittedly should be manufactured to reduce the lead content as much as possible, and a lot of the industries take measures to precipitate the mind calcium to reduce the lead levels. But maybe not expect purity to the point it increases cost to the consumer because keep in mind that the calcium that they ingest enhances the benefit-risk ratio by reducing absorption of lead.

Calcium is one of the nutrients most likely to be deficient in the diet. It was listed as a shortfall nutrient for both children and adults by the 2005 Dietary Guidelines for Americans report, a committee for which I served as a member. Thus, it would not be a health advantage to eliminate calcium supplements using mind calcium carbonate which happens to be the cheapest and most abundant source for calcium supplements.

I'm happy to answer any questions or serve as a resource if that should be welcome.

MR. MORRIS: No, absolutely. And if anybody would have any questions of Professor Weaver, please signify. Marilyn and then Mel.

MS. MORRIS: Just a general question. It's Marilyn Morris. Do other -- are there any other electrolytes that have been shown to also affect lead absorption, such as magnesium?

MS. WEAVER: Yes. Several minerals that are sort of bone seeking nutrients do interact. And that would include magnesium and zinc. So also -- my expertise is calcium, so I can best address that.

But there are other nutrients that would suppress absorption of lead as well.

MR. KOCH: Mel Koch. That's basically the same question I was going to ask because sometimes you have a large interaction between a number of minerals that are co-factors, etcetera.

MS. WEAVER: Correct.

MR. KOCH: Assisting in activity as well as absorption.

MS. WEAVER: Correct.

MR. MORRIS: I'm sorry. I just have one quick question.

MS. WEAVER: Sure.

MR. MORRIS: So to follow up on both those points, are the levels are magnesium safe, say for example, that are natural in mind calcium carbonate dissimilar to lead, or less than lead, or do we know? I know that's not your specialty.

MS. WEAVER: No, mind calcium

carbonate sources for fortifying foods or making supplements would have negligible amounts of magnesium or zinc.

That wouldn't be where -- but in the food supply and for behavior to bone they sort of co-migrate.

MR. MORRIS: Oh, I'm sorry. Dr. Au was recused this morning and rejoins us this afternoon.

Sorry.

MS. AU: I have a question regarding the other ions. So is there a way for us to find out? Based on the calcium, I think your diagram, it was clear there is a linear relationship. But what about the other (off mike) ions? Is there a way for us to know based on the content of the other (off mike) ions what sort of absorption can we expect?

MS. WEAVER: I don't think they've been studied to the degree of calcium, so I don't recall seeing similar obvious negative bar graph relationships the way we have available for us for calcium. It's more of an association by survey associating certain mineral intakes with blood level burden of lead.

MR. MORRIS: Marv.

MR. MEYER: You mentioned a couple of times mind calcium carbonate.

MS. WEAVER: Right.

MR. MEYER: Are there other sources? And are they significant sources or not?

MS. WEAVER: Well, most of the committees I'm on prioritize drinking dairy. So we advocate consuming dairy as your primary source of calcium.

MR. MEYER: But as a recipient, let's say, there aren't --

MS. WEAVER: There are a number of other calcium sources all more expensive and lower in abundance. So, the amount you would have to consume in terms of pills goes up weight-wise. So you have calcium lactate, calcium glutamate, calcium sulfate, calcium phosphate, calcium citric malate.

MR. MEYER: I was thinking more in terms of a substitute for mind to get away from the lead associated with the calcium carbonate.

MS. WEAVER: Well, it can get even worse. If you go more back to products from nature that you can't purify as well, so oyster cell calcium, for example, or dolomite or something, that's even worse for heavy metal contamination.

So, how the committee knows at this time is best to measure by ICP mass spec or something. And you can quantitate them. But there's good enough data to say what the effect of co-ingested calcium is. Maybe not so much the other minerals for the lead suppressing effects on absorption.

MR. MORRIS: Thank you very much.

MS. WEAVER: You're welcome.

MR. MORRIS: So there are no other speakers in the open public hearing, so at the close we'll -- let me just read this statement. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public comments.

Okay, so at this point if we could I'd like to return to question 3 to finalize the nanotechnology discussion of this morning. I know in some ways it sounds like we're asking the same question three different ways; however, there are subtleties in each of these that we can, of course, tease out now as we go on.

So question 3 is for regulatory purposes, what elements or factors should CDER consider incorporating into a definition of nanotechnology? So, to couch this in terms of what we had done earlier, we first talked about the need for guidance given the state of understanding. Then, the focuses and now we're talking about, well, if we need to define it before we can get any farther, what are the considerations? What should be considered incorporating into a definition? And I think Mel and --

MR. KOCH: Mel Koch. I guess it's maybe not following with the intent of the question, but it would be nice to see a list of what CDER's experience has seen as important as a template for developing what needs to be considered. But is there some experiential basis for here are the things that normally are thought of or related to generating such a guidance?

MR. WEBBER: Well, I think rather than give sort of a summary of what we found is important, because I'm not sure how long that list would be -- the essence of this question as I see it is more towards if we were to have guidance or develop policy related to nanotechnology, what would be considered within the scope of that? What type of products? What are the characteristics of the products that would be within the scope of that guidance? And how would we decide if we're dealing with nanotechnology or not?

MR. KIBBE: Before we break I said we really have to separate out the difference between a complex dosage form that uses nanosize particles in a unique way from simply making particles when API or something else nanosized. And I think if you're talking about nanotechnology that needs to be watched carefully, it's the first as opposed to the second. So if I was going to define nanotechnology, it wouldn't simply be any particle less than 1 micron or less than half a micron or some number like that. It would be that technology involved uses particles in the nanosize range which are complex and do a very specific function.

MR. MORRIS: I guess I would add -- I agree with what Art said. And I also agree with what you said earlier with respect -- this is Ken Morris, sorry.

Something you said earlier which is the idea that to make that assessment in part what would go into the definition would be these considerations that you're not going to have at hand unless the company has come forward or the sponsors come forward early to share with you what the technology is or what the belief -- or the level of understanding in the technology is. Because on one hand it seems like we ought to have some element of the uniqueness. We need some sort of the uniqueness factor that speaks to what you're talking about. And if it's unique in the sense that if you have a nanoparticle but it doesn't have any impact on the fate, or disposition, or effect, then that may be a distinction without a difference.

On the other hand, if the functioning depends solely on some aspect, whether it's the size or the structure of the particle, then that seems like a distinction that has to be made or included in any sort of a definition. You know, the definition has to include some level of functionality as well. So there's a structure part and there's a functionality. And then whether or not you call it a technology or just the API itself -- I mean, if you take an API and reduce the particle size until it's nano, that may be just a property of the API at that point. The technology used to get there may not be anything unique; whereas, if you have a layered particle or some sort of a more intricate device, that's a different category there again I would say.

MR. KIBBE: Art Kibbe again. That's exactly what I was getting to. Remember the second speaker, he gave us the Noyes-Whitney equation which is more than 100 years old. Okay, so that equation defines what happens when you change particle size.

Thank you. Okay. So that's not a brand new technology. It's pushing the limit of that technology further down. I mean, more than 50 years ago we started micronizing drugs and now we have the ability to reduce that particle size and prevent aggregation by adding a second ingredient. I don't think that's what you need to be dealing with. What you need to be dealing with are the kinds of things that the first speaker talked about where doing a real complex, targeted system. And that is fraught with issues that you need to address.

MR. WEBBER: What I think I hear you saying is there's a distinction between nanoparticles and nanotechnology. Just because it's small doesn't make it a technology.

MR. MEYER: Perhaps it's a dopey idea, but maybe you could define it in terms of what it's not.

It is not a conventional particle size. It's not a conventional this, conventional that. So if it's not one of those, then it must be -- and produced in a certain way perhaps -- then it's nanotechnology. Because it sounds like, you know, as soon as you get your guidance and your definition out there, somebody is going to come up with something a little bit different that doesn't really fit that. So you're going to be constantly trying to revise or have arguments that they don't fit.

MR. WEBBER: I was just going to add for thought to think about is one of the difficulties we run into is that nano particles or what might -- if you broaden the definition of technology that we deal with is that it's not always intended. You may have a particle that's a nano particle. It wasn't intended to be a nano particle. That's just what it is. And how much do we need to be concerned about those things that aren't necessarily intended to be.

From a scientific respect, if you would think, well, once the body sees it, it doesn't really matter whether it was intended to be a nanoparticle or not. It's going to have the same issues. And those are things we need to consider in developing these definitions.

MR. MORRIS: I think it was Harriet and then Mel.

MS. NEMBHARD: I'm reflecting on the idea that there's a distinction between the simple process for manufacturer and the more complex process for manufacturer, but I'm not sure that is incorporated into a complete definition of nanotechnology. From the standpoint, for example, we've heard presentations about the use of nanoparticulates of gold and silver, fairly well known, well established particles. However, if you are desiring to reduce those particle sizes to some specific dimensions, it may require some processes.

For example, modifications to the wet milling process that may use tooling or tools made out of materials. The point was made that the milling machine should be of 3/16 stainless steel. But if you were trying to reduce the particle size and wanted to experiment, for example, with using ceramics in the tooling, well that may then -- even though the product is simple -- may still want to -- may still call for us to take a look at the product development itself in terms of its nanotechnology relevance.

MR. KOCH: Mel Koch. Just reflecting back reminded me of something that Keith was talking about. At some point there are industrial processes. You go back maybe 20 years ago when you were effectively separating particles based on screening, and there was a certain amount of material that would go through the last screen and would just not only be called dust -- and depending on the product use there was a certain amount of dust that was allowed in the products, whatever. But it often contributed to sticking or other problems in formulation. But it also turned out that it had some effects in actual absorption.

And taking a look on this particular product, there was only like 2/10 of a percent that made it through that last screen. But it had more surface area than the other 98 percent. So there were things that, I think, just happened that, I think, now beg some attention to what are the implications.

MR. MORRIS: Liz.

MS. TOPP: Yeah, Keith, I want to address some issues that you raised a few minutes ago, and I think certainly one thing that a definition would require is some comment on size. But beyond that this idea of structure or in particular, periodicity in structure, this intentionality or periodicity in par t, because the periodicity in a nanoparticulate may be exactly the thing that is an immune stimulant or may, you know, be something that's triggering for that kind of response. So, some other people have talked about, you know, sort of intentionality or structure. These all kind of are the words around the same kind of thing. To what extent is this structured, or periodic, or intentional, as opposed to being dust that happens to be at the nanometer scale or a particle that's really not particularly structured but just happens to be at that size range.

MR. MORRIS: That's really interesting, actually. One comment before -- unless there are others -- before we sum up. All right. One of the things I'm sort of hearing and maybe we can put this in a form of part of the consensus and then query ourselves on it, is that there's still a distinction between -- and I'm not sure where it would go. It would go more maybe in the other question, but it leads into here -- is whether or not we're talking about an existing product that we're changing so that something like that unexpected might show up versus a new product that might go through the rigors of the IND and first in human, you know, that Jerry was talking about earlier, that might not be the same level of scrutiny that you'd give to a product that you were just altering sort of, to your point, I guess, Art.

So I just wonder if in that definition consideration exercise there shouldn't be this inclusion of an altering of an existing product where we think we know what's going on versus a new product.

MR. WEBBER: Yeah, I think along those lines, sort of counter opposed to Art's comment, one of the things that people say about nanotechnology is that once you get to a smaller size you get new characteristics, new functionalities, and new activities for a compound which it doesn't possess when it's a larger size. And those are the things that we need to keep in mind as well. Where and how do you recognize a new activity or a new characteristic based on simply size.

MR. MORRIS: Anything else? Now, let me try to see if we can lasso this into something like a consensus. One of the things I think that comes out of this is that whatever comes of the definition, the definition has to include consideration of the idea that the functionality of what's being done has to be part of the scope of the definition. In other words, if you're just making something smaller for the sake of making it smaller -- I can't remember who said that -- and it doesn't impact on the functionality, then does it really matter? Maybe I said it. Maybe that's why it sounded familiar.

In any case, the idea that you're tying the nano aspects of the dosage form or the product to its activity -- to its functionality -- should be one of the issues -- one of the areas -- elements or factors. One of the elements or factors that we should distinguish between existing product that is to be altered and new material. Not to say that one or the other shouldn't be subject to the same level of scrutiny, but rather that if we don't know the characteristics of what's out there, then how do we know when it's changed, number one; and number two, how do we then determine if there is a difference.

And then in that same vein, Harriet's point about the fact that modification of equipment may -- and the process itself, I guess, in the more general sense, may impart different properties than you know or understand. So, Mel's dust, for example, may be quite a different beast than it was when it started, and then elements like Liz's point about the periodicity perhaps being what stimulates the immune response becomes an issue.

So, if we sort of boil that down a little more, the idea is that we have to know what's in whatever it is we're talking about. So the definition has to start with the presupposition that there's been sufficient communication to allow the agency to know what the product actually consists of and what the level of understanding is. To become a nanotechnology, it also has to be tied to the functionality, and that that functionality may be an intended or unintended result of the process, and then the distinguish between existing and new product. Have I missed anything? Please, Harriet.

MS. NEMBHARD: I may just like to clarify my thought about the functionality. I don't think that a consideration of its functionality -- whether it be a simple function or a previously known product -- should exempt it from coming under the definition of nanotechnology if it meets the standard of a small size -- less than one micron or what have you. Even if it's familiar, if it's of a nanosize, I think that should be sufficient to take a look at it under the definition of nanotechnology.

While I agree the functionality is important, I don't think that being able to say that it had a previous form or a simple function should exempt it from being considered a part of a nanotech product.

MR. MORRIS: Yeah, I guess -- sort of what I was thinking is that you have a structural element and you have a functional element. So structurally it can be a nanoparticle, but functionally, whether or not that makes a difference just in terms of the definition. But I agree that once it's best -- once it's proper scale of measure is a nanometers, then it's nanotech. That's interesting.

Is there anything we've missed in our overview? No? Is that good? Okay. Well, if there's no further discussion we'll go on to Topic 2. We've already heard some from Connie Weaver on this as background, so we should have that in mind as well. Topic 2 is lead in pharmaceutical products. And we're going to -- Norman Schmuff, who is the branch chief division of Pre-marketing Assessment II, ONDQA from FDA is going to give us a historical background and an introduction to the topic. And of course we've all had the pre-reads. I saw Norman. Where did he go? You moved.

MR. SCHMUFF: Thanks, Ken. So, it's my job to cover a little background of how we got here and to give you at least a few specific numbers to think about.

MR. MORRIS: Nice try, but you have to stand up.

MR. SCHMUFF: Okay. And this is sort of the generalized question -- what further steps should we take regarding lead content, specifically in pharmaceutical products. I will mention that we, of course, are representing CDER. And there is another big stakeholder in this, and that's the Center for Foods. And we do have them represented here today. And Dr. Kashtock will be a speaker.

Initially we got a docket submission related to a monograph. And the monograph essentially proposed that for ibuprofen and a number of other drugs -- that we regulate those by a monograph system instead of the current NDA system.

You may or may not know that there really are two ways to do what we used to call OTC and nonprescription products. One of the monograph rail and one is the NDA rail.

So there was a proposal -- a

tentative proposal -- to include ibuprofen. And Albemarle raised the issue of lead in foreign-sourced drug substance and reported some testing that they did. They tested 30 products and here are the numbers for the 1200 mg maximum daily dose of ibuprofen. Okay, U.S. products from not detected to 1.25 micrograms. And the foreign products from not detected to 13 micrograms.

Probably related to this, the Department of Veterans Affairs asked FDA to test some ibuprofen in 2003. And at that time an FDA lab tested 11 samples from two suppliers that came from the stocks of the Veterans Affairs. And really found that there were submicrogram levels -- nanogram levels -- for 1200 mg of ibuprofen.

Just to give you an idea here what the USP limits are like for 1200 mg and a theoretical tablet of, say, 500 mg in weight -- you can read the numbers there. But the result is that you could have as much as about 75, 78 micrograms of daily intake that would be permitted under the current USP lead limits. And that actually -- ibuprofen doesn't have a lead limit. It has a heavy metals limit. And you'll hear a little bit about that later on.

Here's just a summary of some regulatory lead limits. The USP as you'll hear currently regulates on a monograph by monograph basis and with quite a wide range in parts per million (ppm) that would result in quite a wide range of potential daily intake. How CDER does it I'll mention in a moment. CFSAN recently -- that is the Center for Food Safety and Applied Nutrition recently revised their limits on candy to 0.1 ppm. I don't know how much candy you think your kids would be able to eat, but for 50 grams of candy that would be about 5 micrograms intake.

Just for comparison, the EPA -- which does recognize that there is no safe threshold and their goal is zero -- nonetheless has a limit when you have to take some remedial action of 0.15 ppm. So, for 2 liters of water that's 30 micrograms. And the EU foods actually has some limits that really are pretty widely ranging. And I believe that highest limit -- the 1000 mg, or 1000 micrograms, or 1 milligram I think is for bivalves, as I recall.

How does CDER control lead? Well, really it's indirectly via the USP/NF monographs. And about half the drug substances and excipients have either lead or heavy metals limits. And drug products -- very few of the drug products have limits. Just a few of those. And generally we would have no additional controls unless the product contains metals other than sodium or potassium. So generally if we did see these mined elements, metals, we would generally see or ask for a limit on heavy metals.

In '93 there was a provisional

tolerable total intake level that was arrived at by one of the models for lead intake and its correlation with problematic blood levels. And you can see what those numbers look like. So 6 micrograms to 75 micrograms for adults.

And here just, you know, I only went up to grams a day, but here's the kind of range you would see depending on how many parts per million were allowable in a drug product ranging up to 8 milligrams. So you can see that you get up to -- you know, you get up to 75 microgram levels depending on the amount of drug intake and the amount that's permissible. But recall that so far as I reported what we've seen it's more like in the low single digit microgram numbers.

So we did form a working group that was comprised of people from a diverse range of offices.

We knew we had to get some pediatric input. The ONDQA had me as a member. The Office of Pharmaceutical Science, Janna Malay. And there were a couple of people from the OTC group which is now known as the Office of Nonprescription Products. And at some point then we stepped back a bit from the specifics of lead in ibuprofen and merely responding to the lead in ibuprofen and saying, well, maybe we should take a risk-based look at all pharmaceutical products and just see what kind of lead levels we do see.

And I think we came up with a pretty good risk-based sampling plan that also Dr. Kauffman will discuss a little more. So the idea was anything with a mind comp component -- non-alkaline metal -- that's used in the pediatric population and if it's a high volume product. And so we sampled based on that kind of plan.

Now, I'll just remind you that vitamin supplements and minerals are regulated not by CDER but by our Center for

Foods. And there was a letter that was sent by Congressman Waxman in response to a finding that there was 15 micrograms of lead in 2 tablets, which presumably is about a daily dose of a vitamin supplement. Now, there are some -- in response to that, CFSAN collected more than 300 samples of vitamins and minerals, and at least the preliminary analysis suggests that there really are no significantly elevated levels of lead. But you won't see the final levels until that information is finalized.

So, here's the agenda then. First we'll start with medical effects. Then John will talk about the drug product survey that was done. Dr. Abernethy from USP will talk about the USP controls. And I think more interesting, where the USP is moving in this direction. And then Dr. Kashtock will tell us a little about CFSAN's approach to controlling lead exposure. And then we'll have a wrap up and the questions.

So it's a general question that's posed to the Committee. And there are some underlying implicit questions. But the explicit question is what additional information would be necessary for us to gather so that we might appropriately determine the next steps that the FDA or CDER should take.

So, with that, I think I would introduced Susan Cummins, who actually has a fair amount of background in this particular area. And we really were fortunate to have her on the committee because of her expertise in this area, and also her involvement with pediatric drug development at FDA.

So, Dr. Cummins.

DR. CUMMINS: Good afternoon. And thank you for having me.

This is a huge topic and I can only in the time allotted touch the highlights. How do I go forward here? There we go.

I'm going to spend a fair amount of

time talking about the blood lead level distributions in the U.S. population and special groups that we're particularly concerned about and trends about those over time. I'm going to spend some time talking about measurement and modeling the exposure because in the last 15 years or so with the advent of the K X-ray fluorescence machine, which is a tool that's used for research to measure lead concentration in bone, there's been a lot of work in modeling lead exposure and understanding where lead moves around in the body once it's there. And the bone is a long-term storage compartment. We now understand it's interplay with blood lead levels over time.

I'm also going to just touch on -- very quickly walk through what we know about the major health effects, particularly with low level population level exposure.

Oops, sorry. So this is a slide. You can actually go to the Arctic snow strata and burr down like with rings in a tree and collect samples and measure how ambient air lead levels have changed over time. And that's what this slide is showing you. And you can see that starting with the Industrial Revolution there was a gradual increase.

And then the ambient air lead levels really shot up beginning in the 1930s and through the 1950s with the use of leaded gasoline. Leaded gasoline's phase-out started in 1975 and ended in about 1996. And that dotted line is a hypothetical line showing a decline. The amount of tonnage of lead mined each year continues to increase, so if we were able to go and update this slide we might see some interesting patterns.

This is old data but still relevant. This is from the National Health and Nutrition Survey from 1991 to 1994, and it shows you the distribution of blood lead levels according to age and gender. And you'll see a couple of important points I want to point out. The first is that there's this u-shape distribution. So very young children are at high risk, and gradually their risk of lead exposure declines as they get older until they reach adolescence. And then you see a steady increase. You don't really see a gender differential until adulthood, and that's because more men than women work in lead occupations. And most adult exposure to lead is from workplace exposure.

Pediatric patients -- I always like to think of lead poisoning as an opportunity that's tied into development. So the peak age incidence for lead poisoning in young children is around the age of two. At about two they stop engaging in much oral motor behavior. They start talking more. They're exploring their environment less with their mouths. They're being less exposed to lead contaminated dust, and that's why their blood lead levels tend to drop.

We also -- this is just looking at children's blood lead levels over time. And you can see that with each successive NHANES survey there's been a steady decline in geometric mean blood lead levels. This is just in children. We would see probably the same pattern in adults. And that's because of the many environmental and regulatory interventions that have been taken to reduce the amount of lead in consumer products, and gasoline, and paint, and other sources.

This slide, just very quickly, lists the sources -- common sources for adults and children. And for pediatric patients, the exposure sources have changed some over time. We've made a lot of progress in reducing the number of homes in the United States with deteriorated lead based paint. Children can also be exposed when their parents bring lead dust home on their clothing, through folk remedies, through ceramic pots and toys, and many others. And as you know this has really been in the news recently with imports from China that have lead in them surprisingly often.

And there had not actually been a death from lead poisoning in the U.S. until the last couple of years. And there were two children who have died. The first died from lead-based paint exposure, a very deteriorated home. And the second child died because he swallowed a lead trinket that was on his tennis shoe that was imported from China.

Adult lead exposure is primarily through occupation, also through hobbies. They also may use folk remedies that are imported from other countries that have high lead content. Ceramic pots can leach lead. Food can be contaminated. There are many, many sources of lead. It's a very industrially useful metal, and that's why you can find it so much and why people continue to use it.

Now I want to move on and talk about uptake distribution metabolism excretion. There are two primary routes of lead exposure: Inhalation and ingestion. And the only particles that make it into the lungs are the very tiny ones, less than 1 micrometer in size. And those are ones that are respirable. Ones that are inhaled that get stuck in the nasopharyngeal tract can be ingested because they mix with mucous that is swallowed.

Ingestion is the other common pathway for exposure. A little bit can be exposed, particularly from organaleg compounds. Exposure to those now is very rare. And absorption is influenced, as was mentioned earlier, by the presence -- or absence of other nutrients. Iron deficiency, calcium deficiency -- both tend to increase lead absorption. And children tend to absorb more of the lead they are exposed to than do adults. And that's probably primarily because they are at higher risk for those nutritional deficiencies and because they have a much higher metabolic rate.

Now, this is a very simplistic slide, but I want to try to make a point when you think about exposure and cumulative exposure. There are two kinds of ways that particularly children are exposed. You can have a brief acute exposure. Child swallows a BB. Child goes fishing, sucks on fishing weights. Parent has a minor exposure that comes and goes. And you can actually track that by monitoring blood lead levels. A famous example was one a couple of decades ago. There was a big party at the U.S. Embassy in Mexico, and the children's punch was in a lead glazed punchbowl. And the punch was acidic. The lead leached into the punch. The children got lead poisoning, and they all got serial blood lead levels and you could see their blood lead levels go up and go down fairly quickly.

What's much more common and of much greater concern is the kind of chronic long-term exposure that's modeled here where a child was living in a home with contaminated dust, and they are constantly exposed to that lead-contaminated dust because it's from the friction surfaces on painted surfaces. And they are constantly exposed, and over time build up a body burden of lead that is stored in their bones. This is what we worry about the most because once that lead is in that bone compartment it's hard to get it out. It does come out but very, very slowly.

Here is just another slide that goes into a little bit more detail about uptake disposition and excretion. As I mentioned you can inhale it or ingest it. It comes into us. It goes in. Some of it is excreted in feces, sweat, hair, and nails -- a small amount. Most lead then goes into the blood compartment. It mostly is bound to red blood cells.

It interacts with the soft tissue compartments. The ones we worry about the most are the kidneys and the brain, especially for young children. It's primarily excreted in the kidneys, and there's this interaction in the bone compartment.

Most lead over long term is stored in bones. The bone lead body burden for adults is about -- 90 to 95 percent of their total lead burden is in their bones, and for children that number is about 80 to 95 percent.

Now, circulating lead -- there are times when lead levels will go up. There's a tendency when there's a need to heighten bone reabsorption and mobilize calcium. That occurs during pregnancy and lactation. It can happen with prolonged bed rest. For example, children who get a femur fraction and traction actually can become hypercalcemic because there's a lot of bone reabsorption going on just from not moving -- being in bed. Osteoporosis -- post-menopause osteoporosis is a time when that occurs. Hyperthyroidism and weightlessness. Not a common risk factor but one I listed here for completeness.

Now, clinically when you worry about lead poisoning and do screening programs for lead poisoning, primarily we measure blood lead levels. And a blood lead level reflects usually recent exposure. The half-life of lead in blood is about 35 days, but if there's this kind of long-term chronic exposure pathway that I mentioned earlier, the clearance of that lead is not simple. It interacts with the other soft tissues that we worry about and then it equilibrates with soft tissue and bone.

And we kind of always thought this, but this has actually been very well characterized in the last decade with the availability of x-ray fluorescence to measure lead in bone. And I keep coming back to that because this is a real breakthrough. I think the '90s we learned a lot about how to remediate lead in housing, and in this last decade we've learned a lot about how to better look at lead exposure long-term, short-term, and how to integrate the various compartments where it lives in humans.

Bone lead levels are a way to estimate cumulative body burden, particularly -- lead is particularly stable in cortical bone where it has a half-life of decades. A very long half-life. Trabecular bone -- the turnover is more rapid. But still it's years to decades.

There's also been some effort to develop a cumulative blood lead index. And I'll show you an example of that in just a moment. That's the area under the curve -- a way of integrating various blood lead levels taken at points in time to estimate total blood burden.

This slide demonstrates that concept. This is data from the treatment of lead exposed children trial -- TLC trial. It was the only randomized controlled clinical trial of chelation therapy for moderately lead poisoned children. It was conducted in the early- to mid-1990s. Children who had moderately elevated blood lead levels were recruited into the trial. They were treated either with succimer, an oral chelating agent, or a placebo. They were followed for three years to see if there was an impact on their IQ after chelation therapy. And the trial was sized to detect a three point increase in IQ after chelation.

There were many interesting lessons from this trial. Both arms, by the way, had environmental interventions to deal with the lead paint in their homes and to clean it up and keep their homes as free of lead dust as possible. One of the most important lessons is many had hoped in lead poisoning prevention that we could use a decline in blood lead level as a surrogate measure for reduction in lead with chelation. And what we learned from the TLC trial is that wasn't a very useful measure.

You can see that after chelation in the treated group there was a small and transient decline in blood lead levels, but over time there was a convergence between the placebo group and the succimer group. And really, not much lead was mobilized by this chelating agent. It was really an intervention of very limited impact. But you can also see here how one might be able, with a lot of serial blood lead levels, to model cumulative exposure and develop and index of that.

So I'm going to quickly run through what we know about health effects in children. This is a huge topic so I'm going to just touch on the high points. Lead is a systemic toxicant. It's not an essential nutrient. There's no such thing as a normal blood lead level. We have lead in our bodies because it's been used industrially, it's in the environment, and we're exposed.

This slide shows the level of lead in blood is -- on the left side you can see the points when CDC changed their definition of a blood lead level of concern. And you can see also on the right a list of various health effects so that the higher the blood lead level, the more serious the effects.

And we are now thinking about these very low levels. And what's been really interesting in watching lead poisoning prevention and lead poisoning health literature over the years is that as the levels of lead have declined in the population, every time there's a decline then we go to say, well, you know, is there an effect on learning, IQ, cognition, behavior between the range of 0 and 10, which is where the action has been in the last 15 years or so for kids. And we can do that because we can find children with very little exposure as the reference population, and then do comparisons with various levels of exposure.

The effects that we mostly worry about now are these ones here at the bottom -- attention deficits, learning disabilities, school failure, behavior problems, reduced IQ. And I'd add to that that there is literature showing evidence that antisocial behavior and real sociopathic behaviors have been linked to lead poisoning as well.

I don't want to forget mentioning that lead commonly can cause at higher levels microcytic anemia and the symptoms of that -- of lead exposure, such as abdominal pain. And at even more severe levels can cause death from encephalopathy.

This is an old slide. It shows the regression lines for several studies that have looked at blood lead versus IQ. And the important lesson to take home from this is that these lines are all going downward as blood lead goes upwards. And many more studies have been done since this slide was developed, and they would show you generally the same consistent trend.

This is data from -- just to remind me that there have been studies that have specifically looked at behavioral effects of lead. This is one from one of the most famous studies. It was a study of dentin lead levels from deciduous teeth done by Herb Needleman published in 1979. And it shows you that the higher the dentin lead level -- so the yellow is low, up to red is high -- the more distractible, dependent, disorganized, frustrated, unable to follow sequences, and low overall functioning this school-aged child had -- none of these are qualities you'd want your own children to have.

And this was actually -- I want to

give credit to Herb Needleman. I think he's retired now, but he always pushed the envelope. And this was a study that really rattled everyone and moved us in a new direction. He managed to follow up this cohort to graduation and showed, again, that there was a strong and dose-response relationship between deciduous tooth dentin level at age seven, and the likelihood of not graduating from high school -- and in the subgroup that had identified lead poisoning, that likelihood of not graduating was nearly 45 percent. So this is not a trivial effect; it's quite significant.

Now, let's zoom forward. There's been a lot of other research in this area. I want to mention one study that was published in April of 2003 in the New England Journal of Medicine. This was a study by Canfield and colleagues that looked at 172 children. Followed them from birth -- every 6 months from birth to -- from 6 months to 36 months, and then saw them again at 48 and 60 months.

And did IQ studies at 3 and 5 years of age. And then they looked at the impact of blood lead levels on their IQ that was measured and they adjusted for maternal IQ, which is the most positive, strongest predictor of a child's IQ and other co-variants that are related to IQ.

This is their regression line. And you can see a couple of things. Here again is lifetime average blood lead concentration. So he integrated all those values as we discussed. Here are their IQ scores. And you can see that there is a dose response relationship between blood lead levels and Stanford-Binet IQ -- Stanford-Binet is just one of several standardized IQ tests.

And what's important about this one is the action here in the average blood lead levels between 0 and 10. Because you can see that this line -- the slope of this line changes. And that there is a larger dose response effect at these very low blood levels than there is at higher blood lead levels.

Indeed the nonlinear model was the most predictive, and the nonlinear model showed that for blood leads below 10 there was an impact on IQ of 7.4 points. That's about half a standard deviation.

And that for the linear model overall above 10 micrograms per deciliter there's about a 4-1/2 to 5 point decline in IQ for every 10 microgram per deciliter increase in blood lead.

Now, that may seem like a small effect, but it's important when you think about it as distributed over the entire population. If you think that a blood lead level greater than 10 will lower IQ by 2 to 4 points, that has a big -- oops, sorry -- impact on the tails of the distribution. Here and here.

So this little change may not seem

like much, but when you look at the tails it will double the number of children with low IQs in the retarded range, and half the number of children in the high IQs in the gifted range. And the other powerful point about this is this new finding by Canfield that there's a bigger impact in these blood lead levels between 1 to 10 -- that lead has a bigger impact on neurodevelopment as measured by IQ.

I also mentioned that lead poisoning causes anemia. The anemia you see with lead poisoning is a hypochromic microcytic. Red cells -- tiny pale red cells -- that's because lead tends to bind to the enzymes that help to create heme and block its production. And block the binding of iron to hemoglobin, and block the binding essentially of oxygen to hemoglobin. So it mimics and looks very much like the kind of anemia you see with iron deficiency.

It's rare with blood lead levels

less than 35. It's now pretty rate in children because we don't see that that often, but it does still occur in adults.

Other health effects are behavioral effects that have been seen in children and youth in various studies include executive function disorders. That's things like active working memory, being able to plan -- the kind of skills you need to organize yourself and perform well in school as school demands get greater. Complications of attention deficit hyperactivity disorder and school failure. One study showed a very small and subtle effect of blood lead on the date of onset of puberty. There's been studies linking it to dental carriers, and also studies linking it to -- in a small way -- to reduce linear growth.

Now I'm going to move on and talk about adult workers in the general population. And again, lead is a systemic toxicant. It's a dose response relationship in the kinds of effects that you see. Adult exposed workers can have a whole range of health effects depending on their level of exposure.

And with chronic exposure they can have fatigue, apathy, GI complaints, gout, arthritis, impaired concentration, renal disease, and again, microcytic anemia.

The next couple of slides list the range of health effects you can see in adult workers. And I'm not going to walk through these because they're in your slides and you can read them. But only to point out that there are many organ systems involved. And with a high level of exposure, each organ system can experience some damage.

There are reproductive effects that have been reported in adult workers. In males that includes impotence, reduced sperm counts, malformed sperm, and with reduced mobility. For women, menstrual disturbances, sterility, spontaneous abortions and stillbirths. And in both there has been measured genetic damage to germ cells.

Both the National Toxicology Program and the World Health Organization have declared lead to be a probable human carcinogen. The NTP declared it a reasonably anticipated to be a human carcinogen in 2004. And the WHO monograph -- which is if you want a full review of lead and all we know about it, I would highly recommend that document -- found inorganic lead to probably be carcinogenic to humans but was not able to classify organic lead compounds.

The tumors of particular concern are renal, stomach, and brain. There is some data on lung cancer but that's somewhat equivocal.

Now I want to just touch on what we know about the low level exposure in adults. There have been several surveys. I've included a couple of slides from one of the best surveys on these issues.

The reason I want to focus on this is because occupational exposure is regulated in a somewhat different way, but we now know because we can look at where lead migrates over time within the body. There are very well documented studies showing a relationship between low level lead exposure in adults -- much from the mobilization of lead in bone -- and hypertension and renal disease, various cardiovascular endpoints, and cognition declines with aging.

With regard to hypertension there have been many, many reviews and metanalysis of this relationship, including 30 original observational studies. In cumulation, about 60,000 participants that have shown that low level lead exposure is associated with a rise in blood lead levels with every twofold increase in blood lead. So from 5 micrograms to 10 micrograms per deciliter there is an approximate 0.6 to 1.25 millimeters of mercury increased in systolic blood pressure.

And this research has been supported by animal studies as well.

For cognitive function -- now, this is an issue that has just started to come together. There was a large metanalyses published in 2007 that looked at study participants with environmental exposure or current or past occupational exposure. And that's one of the challenges in the adult studies -- is that those two groups are integrated and their exposure stories are often quite different.

These studies supported an association between lead dose and decrements in cognitive function for all these cohorts. And that the kind of effect and cognitive domains include verbal and visual memory, motor and psychomotor speed, manual dexterity, attention, executive functioning, peripheral motor strength. And in each of these studies there appeared to be a dose response relationship.

Now, I just want to mention in closing that much of this research comes from the Normative Aging Study. This is a study that was begun in Boston in 1961. They recruited about 2,300 Boston men. And then to do the lead study, subsetted out 719 men without any occupational exposure history entry. They followed these 719 men over time ever since 1961. They now have bone lead measurements in them, and they've been able to integrate all that data to understand these relationships I've been talking about.

Just to give you the data that they collected from their bone lead measurements -- and you can see it here. They looked at particularly a bone lead burden in the tibia and patella.

So to conclude, lead is a systemic toxicant. There is no evidence for a safe exposure threshold. The integration of bone lead and blood lead measurements has allowed us a more precise categorization of exposure and body burdens over time. And the recent evidence that I just showed you demonstrates that there is harm in children and in adults from low level lead burdens.

Thank you for your time. Do you want to take questions now or do you want to wait?

MR. MORRIS: Actually, if there are clarifying questions then we should take them now if that's all right with you?

DR. CUMMINS: Yeah, that's fine. Absolutely.

MR. MORRIS: Art.

MR. KIBBE: I have just a few that I think you can answer quickly. For people that are not exposed to lead in their workplace, is most of the lead that they have picked up during their lifetime airborne?

DR. CUMMINS: It's airborne or they can also have a point source of exposure. People have things around their house that have lead in it that they don't know. It can be from soldered cans, from a hobby they practice. You know. Rifling enthusiasts pack their own shot. Some people -- my stepmother, who had very poorly controlled hypertension, made stained-glass using leaded solder. I mean, there are many, many ways that adults can be exposed to lead. But occupation is far and away the most common.

MR. KIBBE: Second, your slide 21 shows IQ lifetime average blood level -- it has a curve through it, but the data points are hugely scattered.

DR. CUMMINS: Yes, they are. You're absolutely right.

MR. KIBBE: And what is the reliability of that correlation based on that kind of scatter?

DR. CUMMINS: Well, that's a very good point, and I'm glad you brought that up. I just showed you the most influential and final study that has looked at this relationship. There have been a number of other studies. In the interest of time -- I could give you a whole hour talk on just this area of research -- but a number of other studies have shown a very similar relationship with a very similar estimate of the effect size for blood leads between 0 and 10.

There are many other factors -- one of the challenges is that IQ is an apex measure of cognitive performance. And it's influenced by many factors other than blood lead level. And so the thrust in recent research to look at this relationship has been to collect that data, robust that covaried data as robustly as possible so you can adjust for that. And these are adjusted for those factors.

But there is a lot of scatter. There is a lot of variation in the impact of lead on cognition.

And what the literature suggests is that the children who are most at risk for school failure, who are in the poorest households with the least able parents are the most impacted by this added burden in their lives. Children who are of better economic circumstances, or whose parents are better educated or smarter, tend to recover more from any lead exposure that they had.

MR. KIBBE: Third question. I notice that in the discussion of how lead is eliminated from the body -- because if we have a constant exposure, in order to balance it up and keep our lead levels -- that brings me to the question of what does that mean for the end stage renal disease population whose kidneys have shut down.

DR. CUMMINS: Oh, that's a good question. Well, they are really in a bind. It's difficult for them to mobilize and excrete their lead. You're right. I can't say that I can answer that with more precision. I haven't really focused on that subpopulation.

MR. KIBBE: Because we use calcium.

DR. CUMMINS: Absolutely.

MR. KIBBE: To control their phosphorous level. And if calcium has got lead in it, even if it inhibits lead absorption, it still exposes it. I mean, I just don't know what that means.

DR. CUMMINS: That's a really good question. I wish I could answer it off the top of my tongue, but I can't.

Any other clarifying questions?

MS. MORRIS: In the last study that you talked about the Boston man, I take it they were looking at correlation with disease?

DR. CUMMINS: Yes. A lot of the issues I mentioned earlier -- let me apologize. I should have put those slides earlier in my talk. And I didn't. So I played catch up. But, yes, many of those studies that I cited earlier, much of the data or some of the data came from the

Normative Aging Study. It's been a really
important study in this arena.
MS. MORRIS: So was it mainly
hypertension?
DR. CUMMINS: Hypertension, other
cardiovascular endpoints, such as sudden
death. That data is softer, but there is
some evidence that there is sudden death,
cardiac hypertrophy, other cardiovascular
endpoints, as well. Hypertension is the
biggest one though and the strongest
relationship. And again, a concern because
we all have blood pressure. You know, it's a
variable that's one that's distributed
throughout the population.
Thank you for your time.
MR. MORRIS: Thank you. So next we
have John Kauffman. Is that right?
MR. SCHMUFF: Yes, we have John
Kauffman, who also was a member of our CDER
group, as was Dr. Cummins. And I'd just like
to say that the group could sit around and

pontificate about this issue, but then when it came time to do something about it people always looked to John and said, well, can you guys do this? And as our labs have said in the past -- they always say, yeah, we can do that. And I'll tell you, we had a recent issue in which we had a little project that we thought maybe would be nice to get some data. And that was their response, too. Yeah, we can do that. So, I would say thanks to John, who actually had to set up the assay, validate the assay, buy the samples, and do most of the work.

Also, the paper that came out of this, which Susan was also a coauthor of, really, I think, painted a pretty good holistic picture of the whole issue of lead exposure in pharmaceuticals and the acceptable levels. So, John.

MR. KAUFFMAN: Thank you. You're giving me more credit than I deserve because a bunch of other people did a lot of this work as well. But thank you anyway.

Shortly after the lead in pharmaceuticals working group began to think of broader issues, you know, one of the first things we did was a literature search. And we found that in the literature there was very little known about lead in pharmaceuticals. What's the level of contamination?

And so what I'm going to tell you about today is a survey that we did in the Division of Pharmaceutical Analysis. And I'm going to begin by talking about how the drugs were selected. And this was something that the group -- the entire group participated in. I'm going to talk a little bit about analytical procedures because you can't really talk about lead limits without also considering the procedures -- the analytical methods that are available to test those limits.

And then I'll talk about the

results. And we look at concentrations in pharmaceutical products and materials, and also the amount of lead delivered to the patient by ingesting these materials. And in the end I'm going to relate that to blood lead levels, which is the more relevant toxicological quantity.

So, as Norman mentioned earlier, we used a risk-based approach. And of course, we wanted to address the concerns of the citizens' petition, so ibuprofen was at the top of the list. And we also wanted to look at other analgesics, like aspirin and acetaminophen, and so forth. We looked at calcium- containing, bismuth-containing, other metal- containing products. We figured that those would be the ones that would be most likely to have elevated levels of lead. We also looked at high volume products, and in particular we looked at products that treated chronic diseases like diabetes, cholesterol drugs, drugs for asthma and rheumatoid arthritis. We looked at some over-the-counter drugs, smoking cessation products, vitamins -- which also will have metals in them -- and so forth.

We also attempted to collect imported drugs. We were able to use imported ibuprofen that the FDA collected in routine inspections. But it was very difficult for us to find finished products that we knew with certainty were imported. We found one of those we purchased over the Internet, and you'll see that later.

We were also cognizant of the need to look at pediatric dosage forms. And one of the things -- two of the things I didn't mention up here were that we also looked at products that were likely to be taken by older adults. And also we wanted to have a pretty good balance of innovative products and generic products.

So let me talk briefly about the common methods -- the USP methods for lead.

And there are two of them. The first one is the lead -- a general chapter on analyzing lead. This was a dithazone extraction. You make up a dithazone solution in chloroform and that solution is a bluish-green. And it chelates metals. And when it chelates metals it turns from bluish-green to sort of a bright pink. So it's unambiguous when you're chelating metals. The way you do this is you take your product, and you grind it up, and you extract the metals from it in an acid solution. And ideally you would do this in something like a closed vessel digester. Okay, like a microwave digester because that way you can make sure that all the matrix materials are decomposed and that the lead is truly released. So the best way to proceed is with some sort of closed vessel digestion.

It's a little bit problematic to do that because when you close a vessel and you digest it, you're making carbon dioxide. So it can get very high pressure. So you're limited in how much mass you can put in one of these digestion vessels.

Well, in any case, the dithazone is in a chloroform solution. You take that extract and you extract that aqueous -- that acidic aqueous solution with this chloroform solution, and the lead will partition into the non-polar phase. And then what you do is you take a standard solution and you apply this method. And you take your test solution and you apply this method. And then you look at them and you ask is the test solution more red or less red than the standard solution. And if you answer that it's more red, then you say that it fails the lead test; and if it's less red you say it passes the lead test. And that's the way the test is done.

Okay. The detection limits are in the ballpark of 1ppm. That's probably a little optimistic, but that's the range that it's intended to be used. Okay. There are a number of problems with this. First of all, you have to control pH fairly carefully in order for this method to work properly. It's only useful for a fairly narrow range of analyte concentrations. Calcium, magnesium phosphorous, iron -- a lot of elements will interfere with this test. And it's nonspecific. So if you have zinc and lead in the same solution, you'll get the response and you don't know whether it's zinc or lead. All you know is that the solution turned pink.

It's a fairly elaborate wet chemical procedure. And also you need a fairly large sample mass. The way you increase the sensitivity of this method is to jack up the mass of material from which you extract the lead. And that then becomes too much for a closed vessel digester to handle. And so it's incompatible with the closed vessel digestion.

The other method in the USP that is often used to determine lead or that will often respond to lead in materials is the heavy metals test, Chapter 231. This is a sulfide precipitation. It's also a wet chemical method. You get insoluble colored metal sulfides that turn the solution a sort of rust color, depending on what metals you have. And this is also a similar visual colorimetric test. You have a reference. You have a test. If the test is darker than the reference, then it fails. If it's lighter than the reference, then it passes.

A number of problems with this method as well. The low limited detection here is fairly high for many metals. And it's also nonspecific. It requires elaborate wet chemical methods, and it also requires a fairly large sample mass. And so it's incompatible with microwave digestion. Or it's more challenging to do if you're going to use microwave digestion.

Okay. So these are the two methods that are prescribed by the monographs for analyzing lead and other heavy metals in pharmaceutical materials.

There are lots of instrumental methods available. One of the most widely available ones is a flame atomic emission. And I mentioned for the previous two methods -- the wet chemical methods -- the limits of detection are on the order of a part per million or higher. For flame atomic absorption the detection limit is about 30 parts per billion (ppb).

So that's about 30 times better sensitivity than the wet chemical methods. It's inexpensive -- relatively inexpensive as an instrumental method. It's pretty widely available, and so that's very beneficial because people don't have to buy new instrumentation.

There are interferences that can cause problems. We tried to use this on one of the vitamins that we looked at, and some of the metals really interfere and give you false results. Each metal requires its own specific lamp. So if you want to just do lead, then you just need a lead lamp. But if you want to look at a variety of metals, then you need to use several different lamps. And that increases the amount of time and effort that's required to do the analysis.

It requires a fairly large volume of solution, and that means it requires a fairly large mass of the product that you're trying to analyze. And again, that makes it difficult to do with closed vessel digestion because you would have to do multiple digestions in order to get enough mass.

And there are a number of other methods. Most of the other methods are along these lines. But the state-of-the-art -- the real state-of-the- art is inductively coupled plasma mass spectrometry.

And the detection limits for ICP-MS for lead -- for metals in general -- is in the ballpark of one part per trillion (ppt).

For lead, this is the method we use. We got about a 0.5 ppt. That is, you know, 30,000 times more sensitive than flame atomic emission. So this means we can use very small samples. It's compatible with closed vessel digestion methods, and it's definition the current state-of-the-art for metals analysis.

It's more expensive than AA. This is potentially problematic, but it's being adapted by most analytical labs at this point and the prices are coming down. There are tabletop models and so forth. Not so many interferences because you can separate things out by mass -- single mass unit analysis. And it can survey nearly all the metals.

So this is the method we're going to use. There are a few references on this in the literature, and I think we may hear more about these later. But there was a paper written in 2000 by someone from -- I think this person is from -- well, they're from the pharmaceutical industry. I think they're from Merck. One of these is from Merck, and the other one is from another pharmaceutical company. In any case, this is a survey of replacing the USP heavy metals method with ICP mass spec. And they concluded that this is a much better way to do it. This is another paper that was written also looking at ICP mass spec as a means of screening for heavy metals. And then the third paper here is our paper that was published in 2007. And this is really not looking at the method itself; rather, it's looking at lead in pharmaceutical products -- the prevalence of lead in pharmaceutical products.

So, here's what we did, and this is a summary of our analysis. So we did -- as I said, we used inductively coupled plasma mass spectrometry. Our limits of detection were 0.5 ppb in the product.

Okay. So those detection limits I

mentioned before -- 30 ppb for flame atomic absorption and roughly 1 ppt for ICP mass spec -- that is the detection limit with respect to the solution that you aspirate into the instrument. When you then take into account the fact that you've diluted the sample and so forth, what we get with this method is a detection limit of 0.5 ppb in the actual product. Okay. So we have very good ability to detect lead in pharmaceutical products.

We performed this in collaboration with the University of Missouri research reactor. The analytical services group there -- all they do is elemental analysis. And they are very good at it. They're truly experts in ICP mass spec. And we really benefited from their contribution.

Here's the summary. We analyzed 45 total products. None of them exceeded 500 ppb of head. The highest one we saw was 500 ppb. So, you know, we need to put that in perspective. When Norman talked about what's allowable for ibuprofen, that level would be roughly 25 ppm. And what we see is 500 ppb at the highest. That's about 50 times lower than what's allowable in ibuprofen.

Okay, the average was roughly 50 ppb. That's 500 times lower than what's allowed in ibuprofen. And so I want to emphasize that while I will talk about some higher concentration products versus lower concentration products, those -- I'm referring to high and low with respect to the average of our survey. I would say that none of these constitutes high concentrations of lead in the actual product.

We also looked at 10 foreign sources of ibuprofen. As I mentioned, none of those exceeded 15 ppb. Okay, so orders of magnitude below what we expected on the basis of the citizens petition.

All right, so onto the results. We're going to look at the results along several different dimensions. First we want to look at ibuprofen. So I've tried to color code these. And by the way, this is all published. Okay, so these tables are directly from the published paper. The only part that's not published is this part -- this little bit on ibuprofen API. Okay. And we discussed that but we didn't publish this in a table. And what you see here is that the ibuprofen API -- here are our lead concentrations in ppb. And they range from less than 1 ppb to about 12 ppb. Those are very low concentrations of lead.

I've tried to color code the ones that tend to be on the high side with respect to the products that we looked at. If we see an elevated concentration, I've labeled that with a yellow highlighting. If I see one with elevated intake -- that is if the mass of lead delivered by this product is elevated, then I made that one blue. And if both concentration and intake are elevated, then that one is green.

So, this one happens to be green. The one that we see here that is high is this product that we purchased over the internet. It's a combination product. It contains both ibuprofen and acetaminophen. It has virtually no information on the package about what other materials are in there.

We did X-ray fluorescence analysis on this material to see if we could find calcium because that might be a potential source. There's very little calcium.

We really don't know where lead came from in this product. And yet, it was one of the higher concentration products that we looked at. It's 316 ppb. Still fairly low, but this is one of the higher ones.

So that's ibuprofen. We can look at the pediatric products. And what we see with the pediatric products is that, again, very low levels of acetaminophen. Anywhere from a part per billion to -- most of these down here are in the 1 ppb to 25 ppb range. Those are, again, very low. The highest ones we saw -- actually, this product -- this vitamin product had the highest concentration that we saw. That's right about 500 ppb. The interesting thing about this product is that though the concentration is high, the dose mass is relatively low. And so the mass ingested by taking this product as it's recommended is less than 1 microgram of lead per day.

Another product -- this is a calcium containing product. It had a concentration of 173 ppb. Again, in the ingested mass, if you take it as recommended -- the maximum mass as recommended by the product insert -- you would ingest about.85 micrograms of lead a day. So, I mean, in conclusion, again, very low concentrations of lead in these pediatric products.

Now, I want to focus on the worst cases here -- the highest concentrations.

And I'm going to begin by looking at these. These are now sorted according to their concentration. There are six products that have concentrations higher than 100 ppb. And they range from 500 ppb down to 144 ppb. Most of these are either metal containing, such as this vitamin. There are a couple of calcium containing or bismuth containing materials. So these are things that are expected to have some lead impurities in them.

And then this one down here is a smoking cessation product. And this product actually has a fairly low concentration of lead, but the recommended amount is -- the maximum recommended daily dose is so high that you can ingest a microgram of lead by taking this product as recommended.

So, we can sort these not by concentration, but we can sort them by maximum daily ingestion. And you see that that ranges from about 2.7 micrograms per day down to 1 microgram per day.

Those are the five that deliver the highest mass of lead to the consumer in a day. So the highest one here is about 2.7 micrograms per day.

And we can look at that now with respect to blood lead levels. And this is the same table. I've added this column here. Here's the 2.7. And below I have this table that is -- I believe this is an EPA model that attempts to relate the blood lead level -- the blood lead level to the ingestion rate.

So the toxicologically relevant quantity is the blood lead level, but the easiest quantity to measure is the ingestion rate, particularly with respect to the sorts of things that we're talking about today.

And so the way to think about this is that this is the conversion factor. This blood lead level per ingestion rate. And the units of that is micrograms per deciliter per microgram per day. So you take the micrograms per day that you ingest, you multiply it by this conversion factor, and you get an estimate of the blood lead level. And so we've done that on the basis of the maximum daily ingested mass. And we get these sorts of blood lead levels.

So the blood lead level increase that you can expect from the product that delivers the highest mass of lead is about.11 micrograms per deciliter.

That's the increase. And if you'll remember from the previous talk, the average -- I believe that I got this right -- the average is in the ballpark -- the average blood lead level is in the ballpark of 3 micrograms per deciliter. So that gives you an idea that here we're about an order of magnitude below that. And that's the worst case scenario.

And by the way, this product is a calcium containing product. So we're not